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RADIATION PROTECTION OF THE ORGANISM

(Selected Chapters)

by

S. P. Yarmonenko

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EDITED MACHINE TRANSLATION

RADIATION PROTECTION OF THE ORGANISM (SELECTED CHAPTERS)

By: S. P. Yarmonenko

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U. S. BOARD ON GEOGRAPHIC NAMES TRANSLITERATION SYSTEM

Block	Italic	Transliteration	Block	Italic	Transliteration
А а	*А а*	A, a	Р р	*Р р*	R, r
Б б	*Б б*	B, b	С с	*С с*	S, s
В в	*В в*	V, v	Т т	*Т т*	T, t
Г г	*Г г*	G, g	У у	*У у*	U, u
Д д	*Д д*	D, d	Ф ф	*Ф ф*	F, f
Е е	*Е е*	Ye, ye; E, e*	Х х	*Х х*	Kh, kh
Ж ж	*Ж ж*	Zh, zh	Ц ц	*Ц ц*	Ts, ts
З з	*З з*	Z, z	Ч ч	*Ч ч*	Ch, ch
И и	*И и*	I, i	Ш ш	*Ш ш*	Sh, sh
Й й	*Й й*	Y, y	Щ щ	*Щ щ*	Shch, shch
К к	*К к*	K, k	Ъ ъ	*Ъ ъ*	"
Л л	*Л л*	L, l	Ы ы	*Ы ы*	Y, y
М м	*М м*	M, m	Ь ь	*Ь ь*	'
Н н	*Н н*	N, n	Э э	*Э э*	E, e
О о	*О о*	O, o	Ю ю	*Ю ю*	Yu, yu
П п	*П п*	P, p	Я я	*Я я*	Ya, ya

* ye initially, after vowels, and after ъ, ь; e elsewhere. When written as ё in Russian, transliterate as yё or ё. The use of diacritical marks is preferred, but such marks may be omitted when expediency dictates.

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S. P. Yarmonenko. Anti-radiation of an organism. Atom Press, 1969.

In the monograph extensive material from the investigations by the author and source material on biological shielding from ionizing radiation have been generalized.

Using a cytokaryological analysis of the damage and protection of the bone marrow, convincing proof is presented that the mechanism of anti-radiation protection is the consequence of weakening of the initial damage of critical systems in the organism.

Examined in detail for the first time is the possibility of modifying the effect of various forms of low level ionizing radiation (X-rays, gamma-quantum and protons of high energies) with single exposure fractionated and chronic irradiations. Attempt was made to analyze the dependence of damage and protection of the hereditary apparatus of somatical cells on the distribution of the radiation dosage with time and to evaluate the role of this phenomenon for the immediate and remote effects of irradiation.

The distinctive feature of this book is its practical objectivity of posed problems (application of protective means by man, principles of the hydienic standardization of the radiation factor, etc.).

A wide circle of pertinent problems, their actuality, the critical examination of extensive material from investigations of the author and source materials were calculated primarily for specialists, studying biological radiation effects, and for students of advanced courses corresponding to the college level. Furthermore, the sequence of writing the material, the logical connection

between the chapters, the available method of handling the problems makes an interesting book even for a wide circle of readers, who have no special training.

Page 264, Tables 64, Figures 51, Bibliography 870 items.

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PREFACE

The continuous expansion of man's use of ionizing radiation in various fields of science and technology immerges as the fundamental problem of modern radiobiology in the search for ways of changing radio-sensitivity of the organ. In recent years in connection with the building of powerful particle accelerators and in the development of space research the need arises to solve these questions in reference to new, insufficiently known forms of radiation, specifically to corpuscular radiation of high energies.

One of the practical possibilities of the increase in the radio resistivity of an organ is its utilization as a means of chemical protection - protectors, which substantially reduce the damaging effect of irradiation. During the one and a half decades, which have passed since the discovery of this phenomenon [1, 2], many thousands of tested compounds have been selected to find the most effective ones, capable of preventing death in animals subjected to irradiation in lethal doses [3-5].

The problem of chemical anti-radiation protection has been intensively studied in the laboratories throughout the whole world. Greatest experimental successes in this field have been achieved in our country by P. D. Gorizont, E. Ya. Grayevskiy, T. K. Jarakyan, P. G. Zherebchenko, A. S. Moszhukhin, F. Yu. Nachinsk, V. D. Rogozhkin, Ye. F. Romantsev, P. P. Saksonov, N. I. Shapiro, L. Kh. Eydus, and others.

The practical application of protectors, however, is faced with a number of difficulties [6, 7], associated with both the features of the utilized compounds, and the limited information on their effect under different conditions of irradiation. Therefore, the research towards modifying the damaging effect of ionizing radiation is directly associated with specifying the essence of the radiobiological effect, and allows for unlimited possibilities in future research.

We have undertaken the attempt to do research on certain quantitative regularities of protection and on the postradiation restoration of an organ depending on the effective condition (of the multiplicity of irradiation, of intervals, amount and dose rate) and depending on the physical characteristic of the radiation.

In this monograph the results of the personal investigations of the author and of his colleagues, as well as the data of the joint works with other researchers have been generalized. One takes this occasion to express our heart-felt gratitude to all of them.

I feel indebted to my deceased teacher, I. N. Ivanov, who counciled me in radiobiology. I express my sincere gratitude to P. G. Zherebchenko and I. M. Shapiro for valuable council in the process of completing experiments and even in the discussion of their results.

Work was not free from certain subjectivism in the interpretation of experimental results. This is understandable, if we take into account only first steps of radiobiology, on the whole, and radiation protection, in particular.

By extrapolating the ideas of the known cytologist, Meziya [8] in reference to problems of radiobiology, it can be said that, in attempting to generalize, we recognize the fateful dangers of this course, because the short history of radiobiology knows many examples of various exceptions. It is possible only to comfort boundless perspective of the development of this science, at whose very beginning

we are confronted with all our latest discoveries, and modestly evaluate at least the temporary value of the generalizations as proof of the existence of general regularities, whose exceptions should testify to the fallibility of a made generalization or to to complication of the accepted scheme.

The author with gratitude will welcome critical remarks and suggestions and will take them into account in his subsequent work.

C H A P T E R I

THE MAIN PROBLEMS IN BIOLOGICAL ANTI-RADIATION PROTECTION

The abundance of specialized literature on biological anti-radiation protection precludes the need to examine this problem separately. It is sufficient to merely point out the monographs [9-15] and surveys [7, 16-26] of recent years. In connection with this it is expedient to analyze only most fundamental and unsolved problems facing us.

On should specify from the very beginning that in accordance with the established views, that protection in the strict sense of the word should imply the utilization of protectors only prior to irradiation, having in mind the realization of their effect in the radiation process.

About the Classification of Protectors

One attempts to classify the ant'-radiation means according to chemical criteria, pharmacological features and the mechanism of protective effect.

A classification based on chemical cri eria has been hampered by the fact that, on the one hand, the radioprotective substances which belong to various, distantly related classes of chemical compounds produced an effect, and on the other hand - even an insignificant change in the structure of the compound results in the loss of the radioprotective properties. For example, a

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lengthening of the aliphatic ring in a number of the mercapto-alkylamines [26] or indolylalkylamines [27-32] by more than three carbon atoms results in no protective activity.

It is no less difficult to systematize the anti-radiation means according to pharmacological properties. The pharmacology of protectors has been the object of many investigations devoted to the comprehensive study of the effect of various radioprotective compounds on the nervous system [33-39], gastroenteritic tract [40, 41], cardio-vascular system [12, 42, 43], respiration [12, 42, 44, 45] and other functions of the organs [9, 10, 12, 39, 46-50]. One cannot agree with the attributes of some substances (cyanides, oxides of carbon, hormones, aminazines, serotonins, paraaminopropiophenones and others) of specific pharmacological activity [20] in contrast with other protectors (for example, sulfur-containing compounds), no matter how pharmacological inactive they are. If such a contrast can even be made, then it is only due to the presence of diametrically opposed pharmacological properties in the compounds of these two groups.

Radioprotective effect of tryptamine, serotonin, adrenaline, noradrenalin [20, 51], as well as a large number of indolyl-alkylamines [32, 52, 53] is associated with a vascoconstrictor effect. At the same time β-mercaptoethylamine (MEA) and amino-ethylisothiuronium (AET) at the peak of the protective effect cause resistant hypotonia in dogs [54-56].

The conclusions on the connection of the anti-radiation effect of protectors with pharmacological properties have been also hampered by the fact that the latter has been studied, as a rule, on cats, rabbits and less so on dogs, and the experiments on radioprotective activity has been largely done using mice. Di Stefano and co-authors [57] undertook the attempt to study in parallel the pharma-cological and radioprotective effects of the derivatives of AET on mice. In this case they disclosed that in radioprotective plan the effective compounds (AET, MEA, 3-aminopropylisotiuronium and 3-aminopropyl-1-methylisothiuronium) possess a hypertensive effect,

but the ineffective compounds (2-aminoethyl-1-methylisothiuronium and 2,2'-bis (2-aminoethyl)-1,1-ethylene-bis-isothiuronium) cause deep hypertonia which results in death of the animals. Based on the correlation of the radioprotective effect with time and degree, with the amount of hypertensive reaction, the authors associate the mechanism of protective effect of the indicated protectors on mice, with tissular hypoxia of vascular origin.

The results of polarographic investigations, which have not disclosed a substantial lowering of oxygen pressure in the spleen of mice under the influence of MEA and AET [23, 24] contradict these conclusions.

Thus, the pharmacological investigations of recent years prove the fact that the same protectors in different species of animals cause variable directional reactions, coupled with the fact that their relationship with the mechanism of protection is not always too far removed.

It would be, obviously, more convenient, and more correct to classify the protectors according to mechanism of their radioprotective effect. Unfortunately, the lack of accurate knowledge about the primary processes of the radiobiological effect which is inseparably connected with the mechanisms of protection prevents this. N. V. Luchnik [59] attempted to classify the anti-radiation agents according to the phenomenological principle. Based on the proposals about the dependence of the periods of death on the pathological processes having different latent periods, he studied the effect of 80 compounds at separate periods of death (peaks) and disclosed the selective action of the effective protectors at the first two peaks (on the fifth and seventh 24-hr period after irradiation). Such approach has been doubtledly useful to disclose the mechanism of effect of the separate compounds and especially for its proper combination. Nevertheless, the classification of protectors based on this principle is hampered by the fact that along with the protective agents, in narrow sense of this word, it includes preventive and therapeutic measures.

Thus, some satisfactory classification of protectors is lacking as yet which in itself, proves how insufficiently developed the given problem is, even now.

Despite the abundance of tested compounds in the experiment, most effective and promising of them belong to two large classes - the mercapto-alkylamines and indolyl-alkylamines. The derivatives of these compounds are basically the object of our investigations. At the time of publication of the survey itself [7], which included literature through 1964, and also included material on the correlation of structure and function of mercapto- and indolyl-alkilamines, only individual works, devoted to the investigation of the mechanism of action of protectors appeared. They did not take the problem beyond the point of the more or less argued hypotheses.

Contemporary Proposals About the Mechanism of Action of Protectors

Protection and inactivation of radicals. Starting from the works of Aleksander and Bacq[1] with co-workers [60], who established a correlation between the degree of their radioprotective activity in vivo and in vitro (on a model of polymethacrylate) for more than 100 compounds of various classes, wide acceptance was received from the point of view of the existence of the most general mechanism of the action of protectors, being formulated in a concurrent (relative to a protected biosubstratum) constriction and in the inactivation of free radicals, which appear during the radiolysis of water in cells, primarily of the $HO_2^{\cdot}$ radical. These views will correlate well with the presentations about the leading role of the indirect effect of ionizing radiation and were even considered as a confirmation of this theory. However, with the development of the target theory, the size of the "target" substantially increased [61]. Therefore, one should accept the fact that with the molecules of target in a cell only the radicals, which have been generated inside this enlarged "effective" volume can interact. In this instance

[1]The spelling of this name may appear several different ways. [Trans. Note].

protection by means of the inactivation of the free radicals is not very likely [62], especially since the range of these radicals does not exceed 30 Å.[1]

At present the founders themselves of this point of view also propose to reexamine the significance of inactivating the $HO_2^{\cdot}$ radical in the mechanism of protection, considering that along with the constriction of the radicals there exist two additional possible ways for protection: the restoration of damaged molecules by the existing protector in the medium or by the increase in radioresistance of molecular-targets as a result of their temporary bond with the protector [64, 65].

It is also possible to present a stronger argument against the theory of protection in vivo by means of the simple inactivation of the radicals. First of all from the position of constriction of the radicals broad range of doses of the various protectors is incomprehensible, over which optimum protection is observed. During an equimolecular comparison, they can be distinguished from one another by several orders (cyanides, reserpine 2-4 mg/kg, cysteine 1000 mg/kg). Earlier it was mentioned that the insignificant change in the sturcture of the compound results in the loss of its protective features. This clearly expressed specificity of mercapto compounds in vivo [66-68] in comparison with the data about the approximately equal capability of these substances to inactivate water radicals [69] contradicts the significance of such a mechanism of protection. By the way, based on the data of the supporters of the "antiradical" mechanism, tryptophane, histidine and tyrosine are just as much effective inactivators of radicals, as are tryptamine, histamine, tyramine [69]. However, it is known that in contrast with the latter, they do not possess the protective effect in vivo.

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[1]Such a range of the radical will exist in a situation if each of its collisions appears to be active; if the probability of active collisions is taken as 10^{-3}, then the diffusion already consists of hundreds of angstroms [63].

Recently it is shown that indole, amines of the indole series, and indolylcarbonic acids provide approximately equal shielding from the radiation effect of 5-aminomethyluracil as a result of the expressed ability of indole ring to inactivate the free radicals of water. Protective effect of the shown derivatives of indole in vitro also does not correlate with their anti-radiation activity in vivo [29], which therefore unlikely is caused by the shown mechanism, inasmuch as this is taken into account in the ratio of tryptamine to serotonin [70, 71].

In the opinion of Thompson, the fact remains, contradictory to the hypothesis of the effect of thiols as inactivators of free radicals, that there is the ineffectiveness of their repeated introductions with multiple irradiation. If the problem were to consist only of supplying the organism with a compound, capable of reacting with the free radicals, then it would be expected that their activity would be manifested independent of condition of irradiation, only at a sufficient concentration of the protector in the radiosensitive devices [14]. We found a contradiction to the concurrent hypothesis, under the conditions of multiple action in the absence o the protective effect with a simultaneous lowering of single quantities of the protector and of radiation doses [6].

A serious argument against the radical mechanism was advanced by E. Ya. Grayevskiy [23], who noted that the local intracellular content of protectors is considerably lower than its effective concentrations in the irradiated solutions, and the ability to react with the radicals is unlikely to be higher than in the various cellular metabolites. The contradiction, finally, lies in the fact that the radio sensitivity of ferments, of nucleic acids and of other biologically important compounds is sharply lowered with passage of the solutions to the cell an organ, where their sensitivity approaches that sensitivity in the dry state [72].

Protection and the oxygen effect. The universality of the oxygen effec in various biological systems from a cell to man [73], consisting of the dependence of the damaging effect of ionizing

radiation on the intensity of the oxygen, makes for an intelligible tendency on the part of many researchers, one way or another, to associate the mechanism of effect of the majority of protective substances to hypoxia. In contrast to the concurrent mechanism, the most generally accepted concept, as regarded by Bacq and Aleksander in 1955 [69], and also at the present time, apparently, explains that only individual partial moments of the protection, predominantly in simple systems, for use in the hypoxial mechanism of effect of various protectors have produced much new data.

In [74-82] it was shown that the biogenous amines (tryptamine, serotonin, adrenaline, noradrenalin, histamine, β-phenylethylamine), 5-methoxytryptamine (mexamine), morphine, heroine, carbon monoxide, sodium nitrite, unitiol, dimercaptopropionic acid all cause a distinct change in the concentration of oxygen in the tissues, specifically in the spleen (determined by the method of polarography), based on the time appropriate to its maximum protective effect. For the listed amines this correlates with their vascoconstrictor effect [52]. Based on hypoxia, caused by other substances, there are other mechanisms: the formation of methemoglobin (sodium nitrite, paraaminopropiophenone) or carboxyhemoglobin (carbon monoxide), inhibition of respiratory ferments (cyanides), depression of respiratory center (morphine, heroine), etc.

As confirmation of the pharmacological nature of the effect of the shown compounds and their connection with the oxygen effect there are data available about the possibility of weakening or removing the protection by antagonists or by antimetabolites [52, 76, 83-85] or by increasing the concentration of oxygen [86-88]. On the basis of the anti-radiation effect of hypothermia on homothermic animals there also exists a hypoxiac mechanism, since the protective effect begins to show only after lowering the concentration of oxygen in the tissues below 50% of the original [80, 89].

Recently it was established that the protective effect of dimethylsulphoxide [90], chlorpromazine [91] and chlordiazoepoxide [92] is also associated with hypoxia, and not with hypothermia, in

that the lowering of the temperature of the solid body, caused by these compounds, continues for 2 h and more, whereas the protective effect shows up only in the first 30 min after introduction, i.e., when consumption of oxygen is reduced [92]. The anti-radiation effect of the new pyschotropic compounds, specifically taraktan, are also associated with hypothermia and hypoxia [93].

Consequently, the mechanism of the anti-radiation effect of a considerable number of known protectors in one way or another, has been associated with the oxygen effect. However, in relationship to the large group of thiol compounds (MEA, cystamine and AET) there are discrepancies in the data, the detailed analysis of which was conducted by E. Ya. Grayevskiy and co-workers [23, 24, 93]. A large number of investigations made it possible for them to arrive at the conclusion concerning the independence of the mechanism of the protective effect of cysteine, MEA and AET on the oxygen effect on the basis of the data of a polarographic analysis and irradiation under conditions of an increased concentration of oxygen. At the same time the dithiols (dimercaptopropionic acid and unitiol) caused a decrease in the concentration of oxygen in the tissues.[1]

Along with the data dealing with absence of the effect of the oxygen concentration in the inhaled mixture on the protective effect of the compounds there is also antithesis information [95-98].

Thus far there is no complete clarity, relative to the ways of realizing the protective effect of cystamine. There are much data, testifying to the fact that in an organism it restores glutathione reductases to MEA, which also provides protection [9, 99]. This is confirmed by the fact that cystamine is ineffective during the irradiation of isolated cells [93, 100-103], although it accumulates in them and acquires radioprotective activity after its treatment with homogenate livers. At the same time a series of reactions of

[1]Based on the latter data of the same researchers, if mice breathe oxygen immediately prior to irradiation and even during it, then this lowers the radioprotective activity of the aminothiols [94].

the organism upon the introduction of cystamine has a specific pattern, which distinguished them from reactions with MEA. Cystamine causes the lowering of the concentration of oxygen in the tissues [104, 105], lowers the oxygen concentration in venous blood [106], possesses a hypotensive effect [56], prevents the epilation of hair of the whole skin integument, just as the biogenous amines do, while MEA possesses only a local protective effect with a subcutaneous injection [107].

It is possible that protective activity of cystamine controls both its own pharmacological effect, as well as the partial transformation in the cystamine [24].

Polarographic investigations do not provide a basis for the categorical negation of the connection of the mechanism of protective effect of the thiol bonds with the oxygen effect, based on the fact that the authors also indicate the validity of corresponding investigations [23]. First of all, the contemporary technology of polarographic analysis reflects only sum total oxygen balance in the tissue and does not allow for the measuring of oxygen concentration directly in the cellular organelles, which can have crucial importance in lowering the radio sensitivity. Proof of the fact is that the increase in the oxygen concentration does not completely eliminate the protective effect of biogenous amines (serotonin, histamine, adrenaline), although the oxygen concentration in the tissues in this case even exceeds the normal level [87].

The correlation between the lowering of the extracellular oxygen concentration (recorded by polarography) and its intracellular content does not predetermine the analogous correlative relationships at the increase in oxygen concentration in the medium [14]. It suffices to point out those investigations, in which the protective effect of the thiols apart from toxic effect of the pressurized oxygen [108-113] is shown.

Furthermore, a presentation exists about the presence of the concurrent ratios between the oxygen and the protective substances,

as a result of which the latter can diminish the activated irreversible radiation damage by the oxygen, just as this is proposed in accordance with the data about "the direct" oxygen effect [114-116], the analysis of which was conducted by S. N. Ardashinkov [62]. From these positions in the process of the protection the relative distribution of the preparation and of oxygen in microstructures of the cells acquires crucial importance, which, unfortunately cannot be determined in vivo by existing methods.

Very recently Jamison and Van den Brenk, by using methods of fluorescent analysis of intracellular pyridine nucleotides, giving a rather accurate presentation about the intracellular oxygen concentration obtained very convincing data, testifying to the fact that the protective effect of dimethylsulphoxide and some thiol compounds are not connected with the change in intracellular oxygen concentration [117].

Protection by means of physicochemical change in the biological molecules. The realization of such a mechanism of protection in living cells can be carried out by means of physicochemical changes in the medium (pH, redox potential, ionic force, temperature) or in the chemical bond of molecules of the biological substratum with organic compounds. The shown mechanisms have been compreshensively examined by El'dyarno and Pilo [20], since their own theory of protection by means of the formation of mixed disulfides with tissue proteins most fully disclosed by them, was already proposed in 1955 for compounds of the cysteine-cysteamine group [118]. One should note that the investigations of recent years not only failed to provide evidence of the benefit of such mechanism, but rather provided information of a contrary pattern. Aleksander [64, 65] rejects this hypothesis, since there is no proof of the substantial radiation damage of the proteins and of its role in the radiobiological effect. According to Smollar [119], the lack of a correlation between the quantity of cysteamine in the tissues and its protective effectiveness contradicts the mechanism of mixed disulfide. The maximum protective effect of MEA in mice and rats can be observed 10 min after an intraperitoneal injection, but the maximum content

of the free protector in the tissue of the spleen - after 30 min. These data allowed Bach and co-workers [15, 120] to advance recently the hypothesis about "biochemical shock," caused by the introduction of sulfur-containing protectors as a pathogenetic basis of the very first stages of their interaction with cells in vivo. Here, as proposed, at first there is a combining of protectors with the proteins of the cellular membranes which leads to a change in the permeability of the mitochondrias and their rapid swelling with a subsequent change in the carbohydrate exchange. In favor of the given hypothesis the authors offer only very indirect experimental data [120].

It is easy to show that the disulphide bond can be formed not only by mercaptoethyl- and mercaptopropylamines, i.e., by the effective combinations, but also by their highest homologues; however, as was already indicated, the latter do not possess the protective action in vivo, whereas penicillamine and β-homocysteine are more rapid as radiosensitizers.

Mercaptoalkylamines reduce radiation damage of DNK (deoxyribonucleic acid), not containing sulfhydryl groups which, by the way, will also contradict antiradical theory, because the indirect effect of radiation with respect to DNK may have a preferred value at its concentration in the solution of less than 2% [121], but in the nucleus it amounts to approximately 10% [122].

The insolvency of the theory of mixed disulfides was based on the research in radiation chemistry of mercaptoethylquanidine (MEG) and its disulfide (GED) (guanidoethyldisulfide): irradiation of the mixtures of the latter with proteins results in the formation of the expected decomposition products, MEG and GED [123]. Recently, it is true, that the same researchers arrived at an antithesis conclusion, having shown that in the solutions, containing proteins of 1% and more, their combining with GED always happens by way of the formation of mixed disulfides [124]. On this basis authors allow for the analogous mechanism of protection of GED even at the organism level [124].

In the works of V. G. Yakovlev [125-127] much evidence of the presence of a chemical bond in a number of thiol protectors with the proteins of the tissues of animals has also been presented.

The possibility of a bond of the protective effect of protectors with the shift in the redox potential of the cellular metabolism [128, 129] was considered. In this case no sort of correspondences was revealed between the protective effect of the various metabolites and their standard redox potentials [128]. At the same time in recent years a correlation was shown with time and the degree of protective effect of hypoxia and of certain protectors with a drop in the redox potential in the tissues of insects and mammals [130-132]. Analogous data were obtained earlier by Keiter and his coworkers [133]; however, they observed a drop in the potential in the tissue of the milk gland of rats both under the effect of protective substances (cysteine, cisteamine, glutathione), and under the effect of the radiosensitizer of vitamin K.

The running of these experiments has been hampered, because the nature of potentials, which appear on electrodes are unknown, and because the magnitude of the irradiation itself does not show its effect.

There exist proposals dealing with the fact that the protectors, capable of reducing the oxygen intake, can shield the cell, causing an accumulation of the reduced forms of metabolites, which impart a state of relative radioresistance [134, 135]. Accordingly to these views, essence of the oxygen effect consists not so much in the immediate participation of the oxygen in the processes of radiolysis, but in its effect on the state of the redox systems in the cell. The oxidized state of the latter is radiosensitive, and the reduced state - radioresistant. Therefore, the protection can be carried out not only by the removal of oxygen from the cell, but also by means of utilizing it in another direction [134]. Consequently, in accordance with the given hypothesis, the protectors can shield by creating wither hypoxia or by a change in the cellular metabolism in the same direction, in which it changes the hypoxia [14]. The

tendency in such a theory consists of the possibility of establishing an overall universal mechanism of protection, which in reality, as will be shown further on, is confirmed by many facts.

A Unified Mechanism of Protection

Variation and complexity of an acute radiation syndrome, at first glance, makes the existence of any universal mechanism of protection improbable. Nevertheless, such an assumption has been entirely substantiated [136, 137]. Proof of this are the numerous general phenomenological criteria of the protective effect of the most diverse protectors.

Firstly, they all are related by an obligatory rule - the need to introduce prior to irradiation a reaction of protective response in the very first elementary stages of radiation damage, i.e., during the process of exchange of the energy of radiation. This, by the way, substantially facilitates the perception itself of the possible existence of a universal mechanism of protection, despite the complexity that develops in the subsequent radiation damage. The whole oxygen effect can on solid grounds lay claim to the role of such a universal mechanism. Two general features of protectors serve to play down the argument for such an assumption.

1. The factor of the diminution of the dose [FUD] (ФУД) [Translator's Note: this term and the abbreviation thereof not listed in available references.] of the most effective protectors and their mixtures in the criterion of survival never exceeds 2, i.e., the amount governed by the highest degree of hypoxia, is transferable by animals [14].

2. The effectiveness of a protection, just as the magnitude of the oxygen effect, uniquely depends on the linear losses of the energy of radiation [LPE] (ЛПЭ). With an increase in LPE the degree of oxygen effect [73] and the protective action of protectors is gradually diminished and then disappears [138-140].

In summing up the source material, it is possible to show the following basic ways of realizing the protective effect, in one way or another resulting in hypoxia.

The bulk of biological amines and derivatives of indolylalkylamines has predominantly a pharmacological nature [32, 52, 76, 79, 83-85]. These compounds are, in the main, characterized by a wide range of doses depending on the specific and individual characteristics of the animals.

Serotonin can be related to the typical pharmacological agents. The protective effect of this protector allowing for the molar ratios is found to be 5-6 times in mice, and 15-20 times less in rats, than for aminothiols [141]. Having manifest itself over a broad range of doses [142], in mice it is expressed at a maximum with an injection of 50-100 mg/kg and is depleted with an injection of more than 800 mg/kg [14]. The effect of the protection to serotonin is eliminated by the preliminary introduction of its pharmacological antagonist - 2-bromolysergic acid [75], by means of which the autonomous nervous system is blocked, for example by atropine, phenoxybenzamide and phenolamine [87] and by inhibitors of monoaminoxidase [32, 52]. The convincing data, confirming the actual pharmacological nature of the protective effect, was also produced in experiments in vitro. During the irradiation the suspension of cells of the thyroid gland such substances, as tryptamine, histamine, adrenaline and β-phenylethylamine, do not turn out to have an anti-radiation effect, while cysteine, MEA, cystamine and ethylenediaminetetraacedic acid [EDTA] (ЭДТА) substantially weaken the radiation damage in the thymocytes [143, 144]. Analogous data have also been produced in yeast cells [145]. The exceptions are serotonin and mexamin. According to the data of some authors [143, 146], they do not protect the isolated cells, according to the data of others - their protective effect (in truth, relatively low) does exist [147, 148].

It is possible that the divergences in the results of experiments of the different researchers are associated with the characteristics of the employed equipment and criteria. In some cases the intensity

of the appearances of chromosomal aberrations during irradiation of the cells of Erlich's ascites carcinoma was studied. In this case [AET] (AƎT) (aminoethylisothiuronium) was more effective than serotonin, whose protective effect showed up only in the presence of oxygen [147]. In the others - the appearance of picnoses in the thymocytes was used as criterion [143, 144, 146, 149, 151] or the coloration by the eosin [100, 148, 152] without taking into account gas composition of the medium. One should mention that the data on the protection of the thymocytes generally have discrepancies. Along with the positive protective effect of MEA and of cystamine during the irradiation of a culture of thymocytes [42, 100, 144, 146, 150, 151] AET turned out to be ineffective [149]. According to other datum [152], the clear protective effect was disclosed, when cysteine was applied, *l*-dimethylcystein, isocysteine, MEA and AET, but it was absent upon introducing cystamine, homocysteine, adrenaline and histamine into the suspension, effectiveness of which in vivo, in the opinion of the authors, was governed by the pharmacological reactions.

The estimate of protective response in the thymocytes was hampered by the complex dosage dependence of their death due to the heterogeneity of the population to radio sensitivity [146, 151], which was not always considered in the shown works.

Nevertheless, on the basis of the large amount of data given above one ought to recognize that many protective compounds, including the biogenous amines and serotonin, shield predominantly based on the hypoxial mechanism. In this case one cannot completely exclude the role of their immediate cellular effect, especially in the case of serotonin whose protective effect was even detected on a model of polymethacrylate [60]. However, allowing for the data o. the lack of a correlation between the protective effectiveness of many protectors in vivo and in vitro [29, 153], the utilization of the results of model experiments for an estimate and understanding of protection to animals should be reasonably limited [94, 154].

Considerably more complex is the problem of thiol protectors whose pharmacological effects and effect on the extracellular oxygen

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concentration do not always correlate with their anti-radiation activity.

It is unlikely that one can consider in a random way that in contrast to the above listed compounds, acting predominantly by pharmacological means, that the optimum protective doses of the most diverse aminomercaptans (based on computing) can be differentiated either among themselves or in individual species of animals (by weight in grams) by more than two fold. Obviously, for the realization of the protective effect of thiol protector it is necessary to determine the concentration of the latter in the cell. The magnitude of the intracellular distribution of thiols with an accumulation in defined cellular organelles was distinctly shown by Brandford et al. [155] as an example of a positive correlation between the concentration of the protectors in the microsomes and anti-radiation activity. They found that an equal degree of the protective effect in mice, irradiated at a doseage of 900 R, can be achieved by using bromine hydrates of *d*- and *l*-2-aminobutylisothiuronium and AET with the introduction, respectively, of 2, 4 and 16 μmoles. In this case it turned out that the corresponding products of transquanylization (tagged with sulfur) are equally distributed throughout the organ, but variable in the microstructures of the cell. Specifically, in the microsomes the quantity of the *d*-isomer exceeds the content of the *l*-isomer or the β-mercaptoethylguanidine by two times; with the doubling of the amount of introduced *l*-isomer, its content in the microsomes increases up to the same amounts as that of the *d*-isomer; at this point an equal radioprotective effect is attained. Immediately after irradiation the bonding of the protective preparations in the cellular structures (especially in mitochondrias) is intensified, reflecting its immediate radiation damage. By using fractional dialysis, the authors proved that in the mechanism of the protective effect of the shown compounds there was not formation of mixed disulfides of any substantial value.

By remaining adherents of the antiradical mechanism of protection, Brandford and others treated the data they obtained in their favor, having concentrated all the heat of the controversy on the critic of

the hypothesis of mixed disulfide. Among those same experiments one can even interpret them from the positions of the universal oxygen hypothesis, especially if we focus our attention on the data of Laser [134].

It is possible to present the following sequence, at this point, leading to these events [14]. The thiols, by accumulating in definite critical cellular structures, and being antioxidants, first expend certain amount of oxygen for their own oxidation. This mechanism can act only for a short time, because for the complete oxidation of 50 μmoles of MEA, 1,680 μl of oxygen are needed, and a mouse in a calm state consumes about 600 μl of oxygen per minute. In fact, by considering the lowering of the intensity of tissue respiration under the effect of MEA [156], and based on our own data [157], also confirmed by other researchers [158], and under the effect of cystamine, one can make an assumption about the appearance of a decrease in the utilization of oxygen in the tissues. By the way, Ciccarone and Bacq [158] did not detect an analogous effect on tissue respiration with mercaptoethanol, not exhibiting, as known, any radioprotective features. The weakening of the respiration function of the tissues may be associated with the blocking of the thiol respiration ferments (for example, dehydrogenase of an apple, amber, α-ketoglutaric and pyruvic acids) as a result of the formation of their mixed disulfides with the protector, a fact which cannot be disputed [125-127]. The bonding of the thiols with these ferments leads to a preferential passage of the anaerobic metabolic processes. Under these conditions a disproportion can be created between the extracellular (relatively high) and intracellular (relatively low) oxygen concentration. As a result the redox potential in the cell is lowered, sum total affect of which is reflected by the increase in the reduced forms of the metabolites, specifically the increase in the sulfhydryl[1] oups.

The experimental data, produced in the laboratory by E. Ya. Grayevskiy [94, 136, 159-161].

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It was disclosed that the net gain of SH-groups in the spleen after the introduction of MEA (the determination made in a vacuum or in an inert gas) exceeds their possible number, formed by the protector itself by several fold. An analogous increase in SH-groups was also observed under the effect of hypoxia, when the SH-groups on the outside generally did not materialize. Furthermore, the protective effect of the homogenate of an asphyctic spleen, also containing an increased quantity of SH-groups was detected.

On the basis of these data, E. Ya. Grayevskiy [136] advanced the hypothesis about the existence of a universal mechanism of protection, existing in the tissues under the influence of effective protectors or of anoxia of endogenous highly-reactive sulfhydryl compounds which inactivate the products of radiolysis of organic biomacromolecules. In accordance with this hypothesis, the differences in the radio sensitivity of biological things are likewise determined by the level of the engogenous SH-compounds, performing the role of natural protectors. Certain data which also compare the radio sensitivity of individual cells and strains with the content SH-groups in them [162, 163] are supporting evidence of such a correlation.

Independent of E. Ya. Grayevskiy, analogous views were developed by Reverz [163, 164]. In joint work with Modig it regarded the observed increase in the level of sulfhydryl groups of glutathione after the introduction of MEA into the cellular culture as a possible mechanism of the protective effect of the latter [164].[1]

Thus, it is possible to admit that as a consequence of the hypoxia or introduction of protectors there is a single-type change in the cellular metabolism, governing the state of increased radioresistance. In this plan what is interesting is the correlation between the radio sensitivity of the different lines of mice and the level of oxygen intake by tissues of the same animals, the lowest occurring in mice of radioresistant line and the highest in radiosensitive animals [165, 166].

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[1] An analysis of recent data was given by E. Ya. Grayevskiy in the book "Sulfhydryl groups and radiosensitivity." Moscow, Atom Press, 1969.

Considering the universality of the oxygen response at all levels of organization of living matter, it is very tempting to also extend it as the unified basis of the mechanism of protection. However, the data on the lack of the effect of thiols protectors on the intracellular oxygen concentration in the cells of intestinal crypt [177], which correlate with the sulfhydryl hypothesis of E. Ya. Grayevskiy contradict the examined scheme of such a mechanism.

Attempts to establish the general mechanism of protection from positions of the leading value of the oxygen effect were also undertaken in model systems. Ye. E. Ganasi and L. Kh. Eydus [167], in studying the protection from the radiation inactivation of an aqueous solution of pepsin with the help of AET, sodium pentobarbitol, cystamine, sodium metabisulfite and β-alanine, proposed that the general mechanism of protection consists of blocking a part of the macromolecules by a protector (at a rather large concentration) and also of blocking the access of molecular oxygen.

The data about the unspecific nature of the protection consisting of the blocking the sites sensitive to damaging effect of the oxygen, were produced on plant cells, using β-alanine, [ATF] (АТФ) (adenosine triphosphate) dinitrophenol and chloramphenicol [168, 169], but in the cells of mammals using α-, β-alanine and arginine [170]. In all three works it was successfully shown that the effectiveness of employed agents in relationship to the lowering of the number of cells with chromosomal aberrations did not depend on whether or not they were introduced immediately after irradiation.

The given data is still difficult to extrapolate to the integral organism, because in animals substantial protection based on the same criteria still could not be obtained upon the introduction of protectors after irradiation, although the possibility in principle of this kind cannot be excluded.

Thus, in summing up contemporary proposals about the mechanism of anti-radiation protection, including the considerations of its universality, it is still not possible to decide among the enumerated

hypotheses. None of them either separately or in a combined state can explain the numerous facts, and as was indicated, none carry the intrinsic discrepancies. At the same time during the contemporary state of development of radiobiology the indicated theoretical generalizations should be considered as a useful basis for the logical construction of experimental investigations, the result of which should be valid and which also should dispel the erroneous presentations.

The General Unsolved Problems of Anti-Radiation Protection of an Organism

Beyond the dependence of the mechanism of effect of various protectors at a molecular level, the overall features of the protective effect are phenomenologically most distinctly manifest the cell level and especially of an integral organism.

Enumerated below are those that have been studied and they are the object of subsequent examinations.

1. Chemical protection seems to be effective only under the effect of widely scattered ionizing electro-magnetic radiation. The attempts to use protectors for the protection from densely ionizing corpuscular radiation disclosed a considerable lowering of their activity with neutron irradiation [139, 140] and the complete absence of the protective effect with α-irradiation [138]. The possibility of chemical protection from corpuscular high-energy radiations, [LPE] (ЛПЭ) (linear energy loss) of which approach quantities, inherent of the radiation of an electro-magnetic nature until recently remained unstudied. In this work the results of the study of this problem in reference to protons with an energy of 120-660 (Mev) are presented.

2. In comparison with the abundance literary data on the protection with single exposure there is only an insignificant number of investigations about its application under repeated exposures. In the majority of them the fact is indicated that under these

conditions the protective effect of all protectors is substantially weakened or is completely lost. A special chapter in the way of a monograph is dedicated to an analysis of this phenomenon.

3. The following general feature of protectors is a paradoxical phenomenon - the decrease in the protective effect with the lowering of the dosage of irradiation. As it will be shown, such a conclusion on the whole cannot be considered correct.

4. The general and insufficiently known question is the connection of anti-radiation effect with subsequent restoration, which in protected animals occurs over shorter periods in comparison with control animals, irradiated at the same dosage, but are unprotected. At present two points of view sight exist as to the origin of this accelerated reparation. One of them is associated with the favorable effect of protectors on special systems, responsible for the restoration, and the other envisages the basic reason for the decrease in the initial damage and preservation owing to the cellular background in the basic radiosensitive devices. In the monograph the evidence remaining of the last point of view sight is presented by the author.

5. The qualitative and quantitative criteria used in the majority of investigations of protection is proof of the equal directivity of the protective effect of the various protectors being used as studied indexes (change in LD_{50} (lethal dose), the number of cells of the bone marrow, the number of cells with aberrations, etc.). Along with the data, confirming this position, will be brought material which indicates the specificity of the effect of certain protectors in relation to the individual tissues and stages of the cellular cycle will be presented.

6. No less a general characteristic of protectors is the very weak protection from the wide interval consequences of irradiations, such, as the reduction of lifetime and the appearance of neoformations. On the basis of experimental data about the unequal effectiveness of protectors in relation to the various organs and

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systems, the hypothesis deals with the presence of the irreparable and unprotected part of the damage, the role of which is insignificant in the outcome of acute radiation syndrome, and conversely, it becomes determinable in the development of wide interval time lags.

7. The undesirable general feature in the action of various protectors - the need to utilize them in subtoxic doses, has already been mentioned. This circumstance and particular ones from the just enumerated characteristics of anti-radiation protection are substantially limited so far, but in the opinion of a number of research workers, they make its utilization infeasible for the protection of man. A special chapter of monographs is also devoted to an analysis of the practical aspect of the problem of chemical protection.

C H A P T E R II

REMARKS ON METHODOLOGY

Contradictory information relative to the estimates of radiation doses and of the effectiveness of protectors, to a certain extent, are caused by the heterogeneity of experimental animals, by the unequal conditions of their dosage, and also by errors in the methods of irradiation.

In connection with this, proper experimentation, the results of which serve as an object of subsequent interprelation, as a rule, were randomized by us to the maximum.

The basic data, accumulated by experimental radiobiology, especially in the field of anti-radiation protection, were conducted on small laboratory animals (mice and rats), which, not being highly specialized animals, differed in their relative proximity to the organism of man [171] thereby allowing one to arrange a large number of observations and repetitions.

In special investigations the influence of the conditions of the content of the animals on the effects of irradiation has been established [172, 173], which show up weaker, the less dense the habitat is in the cell, because in this case the mutual infestation and struggle for "leadership" is diminished [172].

In our experiments of trial and control animals they are always housed under equal conditions in groups of 10-20 mice and 10 rats

in a cage. The food ration up to 1961 - consisted of a grain mix, from 1961 - briquetted feed. Water was supplied from automatic drinking fountains.

Methods and Conditions of Radiation Exposure

One of the mandatory conditions of the experiment was the simultaneous irradiation of experimental and control animals and periodic testing of the radiation dose rate. All of the data, presented in the monograph, was obtained in several duplications, the results of which were evaluated not only on the basis of statistical analysis, but also on the degree of reproducibility.

X-ray irradiation. X-ray irradiation was produced on [RUM-3] (РУМ-3) (Medical X-ray Unit-3) or RUM-11 apparatuses under the following conditions: a current of 15 mA, a voltage in the tube of 180 kV, filters of 0.5 mm Cu and 1.0 mm Al, dose rate in air of 35-44 R/min at a distance of 35 cm from the anticathode. Dosimetry is carried out by a condenser dosimeter of the KD-1-M type and by an RM-1 integral roentgenometer. The animals were irradiated in round aluminum chambers, divided into 4 partitions for rats or into 10 partitions for mice. Uniformity of the field was facilitated by the rotation of the chamber with the animals on a specially engineered centrifuge at the rate of one revolution each 3.5 min.

Aside from the systematic dosimetry periodically a bidogical estimate of the dosage is made in special control tests, by determining survival over the dose range of 450-1100 R, encompassing the "marrow" and "intestinal" form of death.

Acute γ- irradiation. The GUBE-800* device with a Co^{60} charge, which produces a uniform field of exposure by means of a circular arrangement of Co^{60} rods and which provides for the varying of dose rate within the limits of two orders as a source of acute γ-irradiation. Mice were irradiated at a dose rate of 270 R/min, rats - at 26 and 64 R/min.

*Spelled out name of this device is not known. [Trans. Note].

Chronic γ- exposure. Chronic around-the-clock γ-exposure of animals was carried out in a specially engineered device with a Co^{60} charge having an activity of 0.0785 g-equiv. of radium. The animals were placed in circular fashion in the cages 10 cm high. The uniformity of the field was controlled by KID-1* and DK3* a micro-r-meter and dosimeters. The dated dose rates of R (roentgen) were compared with the readings of the dosimeters and were calculated according to the formula

$$P = \frac{13,5A}{r^2 \cdot 60} \text{ rad/min},$$

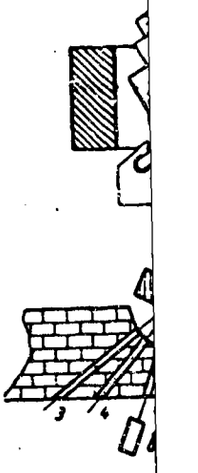
where 13.5 - γ-constant of Co^{60}, rad/h; A - activity of the source, equal to 50 mCi; r - distance from the source to the animals, cm.

By changing the distance from the cages with the animals to the source of radiation (with respect to height or according to the diameter of the field), the necessary dose rate with error of ±10% is obtained.

Irradiation by protons of high energies. Proton irradiation was produced on synchro-cyclotron of the Joint Institute for Nuclear Research (OIYaI) in Dubno [174].

Irradiation was carried out in a collimated pulse beam of protons at the exit of the collimator (Fig. 1) having a flux density of 10^8-10^9 protons/($cm^2 \cdot s$) and an average dose rate of 300-400 rad/min.

Taking into account that the protons are ejected by the pulses (approximately 100 pulses/s over a period of 200-400 μs for each), the true flux density and dose rate in a pulse is 1-1.5 orders higher than the average. Animals were placed (at the rate of 12-15 mice or one rat) in cylindrical chambers having a dimeter of 100 mm (diameter of the collimator), and a length of 15 cm. In order to register the absorbed dose for every part of the animals a carbon plate was irradiated, whereby the induced activity was regarded as



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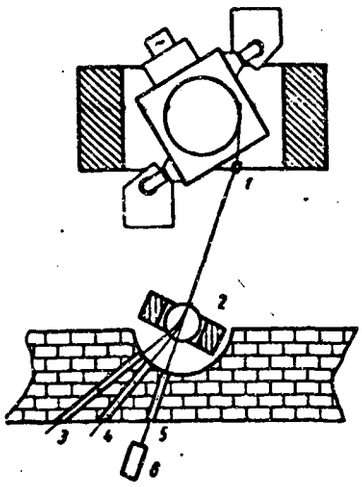

Fig. 1. Diagram of the irradiation in the synchro-cyclotron of OIYaI: 1 - exit of the beam; 2 - SP-37* magnet; 3-5 - collimators; 6 - chamber with the specimen of irradiation. [*Spelled out version not known Trans. Note].

as the flux density, and the density - the absorbed dose. Details of the dosimetry are described in [175].

In order to determine the absorbed dose along with the interaction of protons at 660 MeV in a cell, initially computed values are used according to which the specific absorbed dose is assume to be equal to $5.13 \cdot 10^{-8}$ rad·cm^2/proton [175]. According to other data, it amounts to 4.35×10^{-8} rad·cm^2/protons [175a]. In 1964 this magnitude was produced by A. G. Konoplyannikov in special experiments and hey yielded $4.0 \cdot 10^{-8}$ rad·cm^2/protons [145, 176]. In the majority of previously published literature the earlier quantity of absorbed dose (5.3×10^{-8} rad·cm^2/protons) was used, in connection with the fact that the found coefficients of OBE (relative biological effectiveness) were 1.3 times overrated. Later a corresponding correction [176] was introduced whereby all the material in the given book was also presented.

Criteria of the Protective Effect

During the research on the biological action of ionizing radiation, one cannot give preference to the study of its effect on individual organs and cells, or on the other hand, the investigation of the organism as a whole. It may be necessary to consider a combination of both. One ought only to remember that, by articulating

the individual elementary links of a general complex of symptoms of radiation sickness, it is necessary to actually consider their value at each given moment of time, which can change substantially, by giving way to other pathogenetic elements in another period of a radiation syndrome or to its consequences.

Integral criteria of protection. For a sum total estimate of protection the survival and lifetime of the experimental animals in comparison with the controls, irradiated at the same dosage, but without the utilization of the protective agents are considered.

Four criteria, the advantages and deficiencies of which have been comprehensively analyzed by V. I. Suslikov [177] can be used as such general indexes and they are briefly summarized as follows.

1. The absolute quantity of the difference between survival in the experiment and in the control. This index is convenient at doses greater than an LD_{100}. With a reduction in the dose, when not all of the animals in the control perish, it gives a distorted presentation about the true effectiveness of the protector. For example, if the protector possesses 100% effectiveness at a slightly lethal dose, then the amount of difference between survival in the experiment and in the control will be automatically reduced with the decrease in the dose of irradiation.

2. Index of survival - the ratio of survival in the experiment to the survival in the control [178, 179]. As a quantitative ratio this criterion in no one range of doses gives a correct presentation about the change in effectiveness of the protection with a change in the dose of irradiation. At doses, exceeding LD_{100} in the control, index will be one and the same infinity for both the slightly effective agents, and for the highly effective agents. In the range of slightly lethal irradiation, the index will be automatically reduced with the lowering of the radiation dose, even despite the fact that the effectiveness of protection will always be 100%, just as in the preceding case, having reached the limit of 1.

Both of these criterion, consequently, can only be qualitatively characterized by the presence or absence of the protective effect.

3. The diminishing dose factor (FUD) is characterized by the size of the ratio of two equally effective doses based on their biological action: in the numerator - the radiation dose in the experiment, in the denominator - the radiation dose in the control. For the determination of magnitude of FUD, one must know the survival at two-three radiation doses. The calculation of FUD it has been hampered at the minimum lethal and minimum absolute lethal dose due to the asymptotic proximity of survival to the 100% and zero level. However, in the range of average lethal irradiation, FUD is satisfactory and reliable quantitative criterion, especially if doses, equal to LD_{50} are used for a comparison.

4. Coefficient of protection reflects the probability of protection of an organism, representing a ratio of the difference between the specific vulnerability in the control and in the experiment to the specific vulnerability in the control [177]:

$$\alpha = \alpha(D, A) = 1 - \frac{p(D, A)}{p(D)}$$

where α - coefficient of protection, $p(D,A)$ - probability of death of the animals, irradiated at a dose D under conditions of utilizing the protector A; $p(D)$ - probability of death of the animals, irradiated at a dose D without utilizing the protector.

The coefficient of protection indicates, which portion of the perished animals in the control can be recovered as a result of using the protector. With overall protection, $\alpha = 1$, in its absence, $\alpha = 0$.

Coefficient of protection is a correct criterion, but its deficiency consists in the fact that with the lowering of the radiation dose at a constant FUD value, it automatically diminishes. In the majority of our investigations the FUD was determined.

With the differentiated estimate of the degree of protection from an "intestinal" or "marrow" death, the lethality over 4 and 30 days, respectively were evaluated, conforming to a certain period of time of death, reflecting definite systemic damage [180].

The criterion of mortality is inconvenient for estimating the protection with slightly lethal irradiation due to the high variability and is absolutely unsuitable with sublethal injury. Therefore, it is necessary to use methods of estimating the effectiveness of protectors in separate systems of the organism at all levels of concentration - from sublethal to supralethal [181].

Cellular criteria of protection. Investigations at the cellular level allow for establishing the most general behavioral patterns of the radiobiological effect. The specific value is acquired by the analysis of cellular destruction, which appears during the irradiation of the integral organism, offering the possibility of a quantitative estimation of radiation injury of the latter and the degree of its protection according to the changes in most radiosensitive systems.

In the bone marrow of femoral bones studied mitotic activity, cellular degeneration and chromosomal aberration on the pressed preparations stained with acetocarmine or according to Feulgen's method [182].

For the determination of the degree of degeneration and of the mitotic index there was a miscalculation of 3-5 thousand cells for each animal. To avoid including in the calculation the cellular splinters the degenerating cells are grouped with those having preserved boundaries, whose nuclei have been destroyed by means of lysis or kaksisa, and which are intensively stained, but with undamaged cytoplasm.

During the determination of the number of cells (in percent) with chromosomal aberrations in the form of fragments, or of pons with fragments, or only pons in each mouse 80-100 cells are counted

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at the stage of late anaphase or early telophase. Cells at the stage of late telophase were not considered, since during this period the ejection of acentric fragments of chromosomes beyond the confines of the cells were not excluded and ruptures of the pons were possible [183].

The total number of nucleus-containing cells of bone marrow in the thigh in contrast to the described methods [184, 185] was determined for the femoral bone as a whole, not just in the diaphysis. Both bones of the mice were thoroughly cleaned of soft tissues, ground in a test tube with a 3% trichloroacetic acid solution, stained with methylene blue, thoroughly shaken, and then the number of cells in the Bürker counting were calculated. As a result of calculating the preparations of 40 control mice it was established that as a standard in one thigh bone of a mouse having a weight of 20-24 g, it contains 33 ± 2 million cells. The authors of works [184, 185] did not consider all the cells, undergoing a conformable change in their composition of the segment of diaphysis comprised of 10-15 millions of cells.

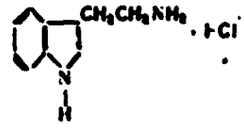
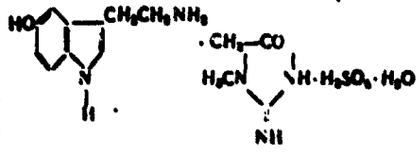
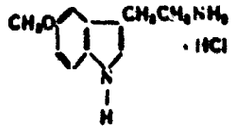
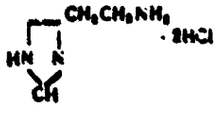
As an additional criterion of estimate of the effectiveness of protectors a calculation of the total amount of leucocytes in peripheral blood was made and less frequently by using the leucocytic formula.

Research on radiation damage in the cells of the liver was made in experiments on rats, by stimulating the cellular division of partial hepatectomy according to Higgins and Anderson [186] with a subsequent analysis of the conventional hystological preparations, stained according to the Feulgen method.

Protectors and Methods of Utilizing Them

Majority of employed protectors (Table 1) are administered intra-abdominally, less commonly internally (with the aid of a probe)

Table 1. Optimum protective dose of the protector based on calculation, mg/kg.

Compound	Chemical formula	Provisional name of the preparation	White mice		Rats	
			intraperitoneal	internal	intraperitoneal	internal
β-mercaptoethylamine, hydrochloride	$HSCH_2CH_2NH_2 \cdot HCl$	Cistsamin MEA	180	—	100	—
β-mercaptoethylamine disulfide, dihydrochloride	$SCH_2CH_2NH_2 \cdot 2HCl$ $SCH_2CH_2NH_2$	Cystamine	150	400	100	225
S-β-aminoethylisothiuronium bromide, hydrobromide	$H_2NCH_2CH_2SC(=NH)NH_2 \cdot HBr$	AET	150	400	80	—
Monosodium salt of β-aminoethylthiophosphoric acid	$H_2NCH_2CH_2SP(=O)(OH)ONa$	Aminoethylthiophosphate (cystaphos)**	350	800	300	600
3-(2'-Aminoethylindol, hydrochloride		Tryptamine	100	—	—	—
5-Oxytryptamine, creatinine sulfate		Serotonin	50	—	—	—
5-Methoxytryptamine, hydrochloride		Mexamine	75*	300*	30	120
Imidazole-ethylamine, dihydrochloride		Histamine	200	—	—	—
Hydroxylamine, hydrochloride	$H_2NOCH_2 \cdot HCl$	QA (Glucosamine)	40	—	—	—

*As they have indicated in recent research, the optimum protective doses of mexamine are 5-10 times less (see page).

**cystaphos - not recognized in U. S. Chemical references.

n calcula-

mice	Rats	
—	100	—
400	100	225
400	80	—
800	300	800
—	—	—
—	—	—
300*	80	120
—	—	—
—	—	—

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or under the skin, in a physiological solution at a volume of 0.2 ml.[1]

The distribution of protectors were studied using as an example aminoethylisothiuronium dihydrobromide, tagged with S^{35} and P^{32}. The synthesis of the tracer compounds was performed by the head of Radiochemistry, Moscow State University names after M. V. Lomonosov and in the laboratory of the Institute of Biophysics.

Distribution of the protectors were studied using as examples, S^{35}-AET, S^{35}-cystaphos and P^{32}-cystaphos.

In the experiments preparations were used with a specific activity of 20-50 mCi/g of S^{35}-AET, 10-15 mCi/g of S^{35}-cystaphos and 1-5 mCi/g of P^{32}-cystaphos. The calculation of the activity was made in a thick layer of tissues and in citrate of the blood.

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[1]I wish to express deep gratitude to academician I. L. Knunyants, Prof. N. N. Suvorov, Doctor of chemical sciences O. V. Kil'dyshev, Instructor P. Yu. Rachinskiy and V. M. Fedoseev and Master of chemical sciences M. G. Lin'kov, R. G. Kostyanovskiy and A. G. Tarasenko for scientific collaboration and synthesis of compounds, whose high quality was one of the determining factors in conducting the experiments.

C H A P T E R III

INJURY TO THE BONE MARROW AND THE MECHANISM OF ANTIRADIATION PROTECTION

Decisive role of the state of hemopoiesis, largely in the bone marrow [178, 187], as a result of acute radiation injury at moderately lethal (up to 1000 R) doses is now universally recognized. This, quite evidently was proven with experiments by screening the spleen or sections of bone marrow [188-190] and by the practice of hemotherapy, especially the transplanting of bone marrow as a method of therapy of acute radiation syndrome of various animals [187, 191-196 and others], including rabbits [197, 198], cats [199], dogs [200, 201] and monkeys [200, 202-204], but as well as man [205-208].

The tendency of researchers to detect a decrease in the degree of radiation damage of hemopoiesis with the help of various protective measures was determined namely in this way. It was shown, specifically that under the effect of protectors in hemopoietic organs radiation injury of albuminous and nucleic exchange [209-215], of oxidizing phosphorylation [213, 216-218] is weakened, the degree of cellular degeneration [219-222], appearances of chromosomal rebuilding [221, 223, 224] and the degree of the overall devastation of the bone marrow [181, 224] is diminished.

Two principle opposing points of view exist relative to the effect of protectors to the radiation injury of hemopoiesis. According to one of them, the protectors do not diminish the degree of injury of the bone marrow, spleen and other hemopoietic tissues, but only facilitate the acceleration of regeneration [225-238].

Thus, it is necessary to recognize the presence of specific hypothetical regenerative systems in an organism. In the opinion of Cronkite [226], glutathione shields the humoral factors which regulate hemopoiesis. Bacq [15] only recently rejected his earlier expressed assumption [230] about the fact that protectors shield some substratum, which stimulate hemopoiesis, or shield, and more accurately, restore cells from damage produced on this substratum.

According to another point of view, protectors reduce the initial damage of hemopoiesis, thus providing them with more intensive reparation later on [23, 24, 220, 239-249]. By completely separating these views, we have derived experimental evidence from them [25, 137, 250-255].

Contradictions exist to this very day. Among them the solution of this problem has fundamental value for the successful development of the problem of antiradiation protection.

In this chapter and further on the results of early attempts, carried out in this direction and also the further development of investigations, which allow for the affirming of valid presentations about the crucial importance of the removal of a part of an effective dose by protectors, and consequently, a decrease in the degree of initial damage of hemopoiesis, will be presented.

Increase in the Radioresistance of an Organism with Local Anoxia of the Bone Narrow

Even at the very beginning of the twentieth century, soon after the discovery of X-rays and of natural radioactivity, the possibility was shown of reducing the radiosensitivity of a section of a man's skin along with a local decrease in the blood supply by the application of ice or by simple pressing [256]. Later a decrease in the radiation injury of separate portion of the thymus of rats and mice [257], of the tail [258] and internal organs [259, 260] was shown by stopping the access of blood by ligature, taking into account these data and the role of bone marrow in the outcome of

acute radiation injury, P. G. Zherebchenko, I. G. Krasnyy and N. P. Lebkovaya together with us undertook to increase the survival of animals by applying a tourniquet during the period of irradiation taking into account the creation of an ischemic section in bone marrow of the extremity below the constricting point [252, 253].

As can be seen from Table 2, during the X-ray irradiation of mice at an obsolute lethal dose, the application of a tourniquet to the posterior extremities controls the time of death of all control animals (12 twenty-four hour periods) and the survival of 75.3% of the experimental mice. Up to 30 twenty-four hour periods the number of surviving animals was reduced; nevertheless, up to this period, the average was 32.6%. An analogous pattern was characteristic even for experiments on rats and dogs.[1]

Table 2. Effect of local anoxia of the bone marrow at the end of radiation sickness of the animals.

Species of animal	Dose of irradiation, rad	Groups of animals	Number of animals	Survival, twenty-four hour periods						Average duration of life, twenty-four hour periods
				12-e*	30-e	12-e	30-e	12-e	30-e	
				Number		%		T		
Mice	700	Control	65	4	0	6,1±0,9	0	—	—	8,4
		Tourniquet on one thigh	72	24	6	33±6,5	8,3±1,2	3,4	0,6	10,7
		The same	98	72	32	75,3±4,4	32,6±4,7	15,0	7,0	14,1
Rats	800	Control	90	37	6	40,7±5,1	6,6±2,6	—	—	11,6
		Tourniquet on one thigh	66	36	16	54,3±6,2	24,6±5,3	1,7	3,0	9,8
		Tourniquet on two thighs	84	53	26	61,4±5,3	30,7±5,0	3,0	4,3	11,9
Dogs	400	Control	13	1		—	—	—	—	—
		Experiment	13	5		—	—	—	—	—

45 twenty-four hour periods

Note. T — degree of reliability

*12-e = 12 twenty-four hour periods

[1]Running the experiments on dogs was hampered by the low power of the irradiators, and was associated with this prolonged pressure of the tourniquet; this caused the development of a shock reaction. To guard against this complication the application of the tourniquet and the irradiation was conducted under morphine (5 mg/kg). However, our investigations showed that the morphine considerably complicates radiation sickness in dogs. Thus, during the irradiation of the control dogs in the state of morphine narcosis even at 400 R a heavy

The death of the animals during the late periods, obviously, was associated with infectious complications, because the additional application of streptomycin during the first 20 twenty-four hour periods (3-5 mg per mouse) caused an increase in the survival up to the 30th twenty-four hour period of 33% on the average; streptomycin itself controlled the survival of only 8.6% of the mice (Table 3).

Table 3. Effect of the combined application of local anoxia with MEA or antibiotics at the end of acute radiation sickness of mice.

Radiation dose, rad	Groups of animals	Number of mice	Survival, twenty-four hour periods						Average duration of life, twenty-four hour periods
			12-e	30-e	12-e	30-e	12-e	30-e	
			Number		%		T		
700	Tourniquet	98	72	32	75,3±4,4	32,6±4,7	15,0	7,0	14,1
	Streptomycin	70	20	6	28,6±5,3	8,6±2,0	5,0	4,0	11,5
	Tourniquet + streptomycin	82	68	54	83±4,0	65,8±5,6	8,0	9,5	12,6
750	Tourniquet	78	40	12	51,3±5,6	15,4±4,3	9,0	3,6	11,3
	MEA	60	37	21	61,7±6,3	35,0±6,2	15,0	5,7	12,5
	Tourniquet + MEA	60	52	34	86,6±4,4	56,5±6,4	3,3	2,4	19,5

The favorable effect of local anoxia is summarized along with the protective action of [MEA] (MƎA) β-mercaptoethylamine.

For an estimate of the effect of functional shifts on the radioresistance, induced by applying a tourniquet, a morphine narcosis or anesthetization of the extremity by novacaine was produced. In this case a lowering of the radioprotective effect was not observed. Consequently, the effect of the tourniquet was not possible to explain by the functional shifts as a result of the algesic reaction. Apparently, the observed effect of protection of the organism basically has been caused by the preservation of

[FOOTNOTE CONT'D FROM PRECEDING PAGE] radiation syndrome developed in them with a fatal outcome. Nevertheless, despite the application of morphine, the application of tourniquet noticeably reduced the degree of injury and increased the survival of the animals.

certain number of undamaged bone marrow; this facilitated the subsequent activation of hemopoiesis. In this sense the results of the investigations of peripheral blood were significant.

As can be seen from Fig. 2, the application of the tourniquet turned out favorably in the leucocytic reactions of the irradiated animals, especially with the additional protection of MEA. A similar intensification of protective effect relative to changes in the peripheral blood was observed when MEA was applied together with general hypoxia, which was attained by chilling the mice [261].

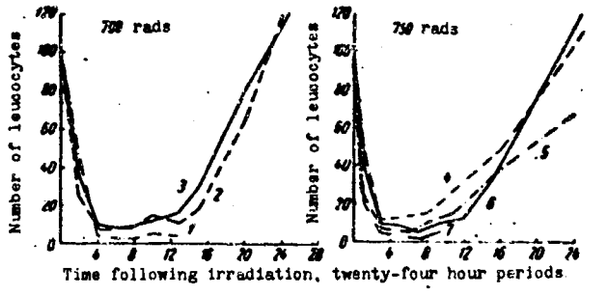

Fig. 2. Dynamics of the total amount of leucocytes in the blood of irradiated mice under the effect of local anoxia of the bone marrow, MEA and streptomycin: 1 – streptomycin; 2 – tourniquet; 3 – tourniquet + streptomycin; 4 – MEA + tourniquet; 5 – MEA; 6 – tourniquet; 7 – control.

The investigation of peripheral blood does not completely reflect the mechanism of protection of hemopoiesis, since the difference in degree of leucopenia for protected and experimental animals occurs over relatively widely spaced periods after irradiation. This also served as a basis for widespread opinion about the fact that protectors have a positive effect only on the processes of regeneration.

Cytological Analysis of Radiation Damage of Bone Marrow

Early degenerative changes in the cells. Fluorescent analysis of supravitally stained preparations of bone marrow of mice and rats, subjected to single exposure in doses of 50-1500 R, confirmed the data [262] about the appearance of micronecrosis in bone marrow in the initial hours following radiation exposure. A similar phenomenon may be also observed in mice, guinea pigs and rabbits, subjected to external Co^{60} γ-irradiation or X-ray irradiation of 90-180 kV in doses of 800-1200 R, as well as in rats, upon the introduction of 1.3 μCi of P^{32} [250]. With local irradiation of the rats it was established that micronecrosis appears only in the bone marrow of the irradiated sections and never develop in the protected extremity; this is proof of the local nature of radiation damage of cellular nucleic structures, just as is also proven in the experiments of N. F. Barakin in the research on cellular destruction [263, 264].

From Table 4 it is evident that MEA retards the formation of micronecrosis in the bone marrow of rats, irradiated at doses of 200 and 800 rads. However, the method of fluorescent microscopy (in its initial variant), has entirely proven itself as a means of early experimental diagnostics of radiation injury, and in a certain degree, the preliminary estimate of protectors, cannot serve as a strict quantitative criterion.

Table 4. Effect of MEA on the formation of micronecrosis in the bone marrow of irradiated rats.

Dose of X-ray irradiation, rads	Group	Number of rats	Number of cases of micronecrosis in 10 fields	
			after 2 h	after 4 h
800	Control	12	18±4	24±5
	Experiment	10	0	19±4
200	Control	8	8±3	16±4
	Experiment	10	1±1	12±3

More sharply defined data were received on the research of bone marrow in pressed preparations.

As can be seen from Fig. 3, under the effect of local anoxia the number of degenerating cells during all periods of observation decreased which is evidence of the less damage of bone marrow in the ischemic section.

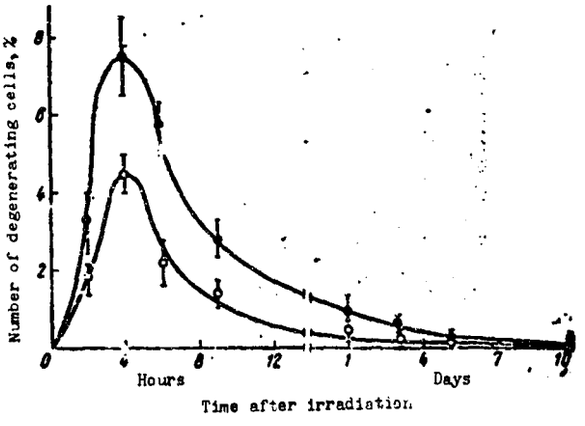

Fig. 3. Effect of local anoxia on the degeneration of cells of the bone marrow of mice, subjected to X-ray irradiation at a dose of 700 rads.
o – experiment (bound extremity);
● – control (unbound extremity).

Special experiments were conducted for the purpose of clarifying the effect of the duration of local asphyxia on the manifestation of the protective effect. Mice (one at a time) were irradiated at a dose rate of 1050 rad/min in a specially designed chamber (Fig. 4), equipped with an automatic device, enabling it at the proper moment with the help of a relay to instantly apply a tourniquet to the thigh of the fixed mouse. The application of the tourniquet was always made to the right thigh, and the bone marrow was extracted from the tibial bones (right – experiment, left – control).

As can be seen from Table 5, a decrease, true to form, in the radiation damage of cells of the bone marrow is observed only with the application of the tourniquet for 2 min prior to the beginning of irradiation.

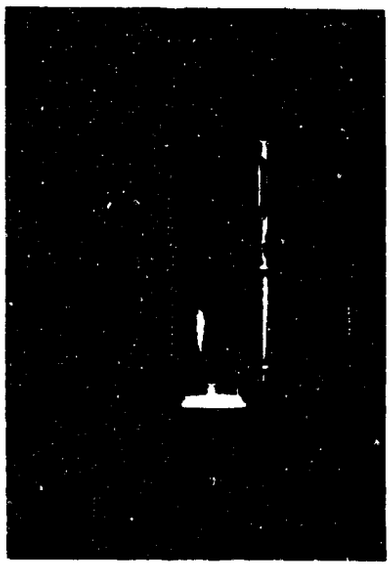

Fig. 4. General view of the chamber with the automatic device for instantaneous remote application of the tourniquet: 1 – automatic starting; 2 – relay.

Table 5. Effect of time of the application of the tourniquet on the degeneration of cellular nuclei in the ischemic section of bone marrow after 4 h following overall irradiation of mice at a dose of 700 rads.

Time of application of the tourniquet	Number of mice	Number of preparations	Number of degenerative nuclei per 1000 normal ones			t
			Control	Experiment	Relative to control, %	
For 2 min prior to the beginning of irradiation.	8	40	200	119	59	4,0
For 1 min prior to the beginning of irradiation.	5	25	194	122	63	2,2
Simultaneously with the beginning of irradiation.	13	42	194	146	75	2,4
Through 10 s after the beginning of irradiation.	15	60	377	386	102	1,2

A shortening of the periods is accompanied by a lowering of the protective effect. Thus, for the manifestation of the antiradiation effect of local anoxia a certain time is necessary, during which a determinable degree of depletion by oxygen of the bone marrow occurs which also affects an increase on its radioresistance.

A reduction in the number of degenerating cells under the effect of anoxia, induced by the application of ligature to a vascular bundle was observed in the spleen of mice [265] with the constriction of the ventral aorta or with the inhalation of nitrogen – in the general lymph nodes of rats [266], with general hypoxia – in the bone marrow of mice, since the effect of hypoxia here was intensified by cysteine or MEA [223, 267] similar only to that in the described experiments with the combined application of local anoxia and MEA.

Table 6 shows data we obtained at a different time as well as in unrelated experiments about early degenerative changes in bone marrow, appearing during the initial hours following X-ray irradiation under conditions of using protectors.

0.23 ± 0.014% of the degenerating cells is maintained in intact animals (biological control) which corresponds to the data of other researchers [268]. After 2-4 h following irradiation, the number of degenerating cells in control animals increases by 10-40 fold depending on the dose. Under the effect of protectors the intensity of the degeneration is reduced.

Table 6. Number of degenerating cells in the bone marrow of animals, subjected to overall X-ray irradiation, %.

Species of animals	Dose, rads	Group and dose of the protector, mg/kg	Through 2 h	Through 4 h
Rats	752	Control MEA (100)	13.4 5.0	24.4 6.0
Mice	188	Control MEA (150)	4.1 1.5	4.7 3.3
	270	Control AET (150)	— —	5.9±0.36 3.3±0.17
	400	Control AET (150)	— —	11.4±0.3 5.9±0.31
	700	Control AAT (150)	— —	12.9±0.99 8.8±0.5
	—	Biological control	0.23±0.014	—

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An estimate of the results of the experiments, given in Table 6, is complicated by the fact that the bone marrow was investigated only during selected periods (during maximum degeneration). A dynamic study of this process for two days after irradiation showed that [AET] (AET) aminoethylisothiuromium reduced the number of degenerating cells during all investigated periods. As can be seen from Fig. 5, at doses of 270, 400 and 700 rads the maximum degeneration occurs at 4 h after irradiation, then the number of degenerating elements rapidly diminishes and even towards the end of the first twenty-four hour period at 270 rads in the 2nd twenty-four hour period at large doses, they are completely eliminated from the bone marrow.

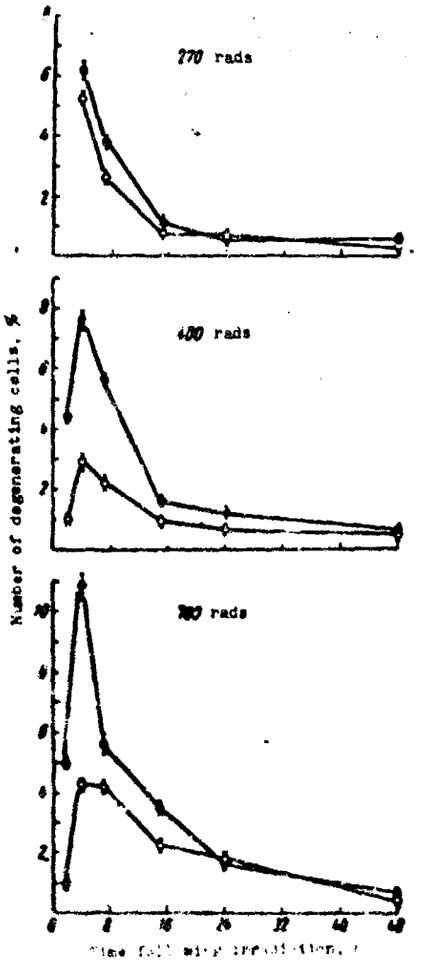

Fig. 5. Effect of AET on the number of degenerating cells in bone marrow of mice at different radiation dose (4-6 mice per point): ● – control; o – experiment.

A quantitative estimate of the protective effect according to the given criterion is hampered by the lack of information on the time of existence of the degenerating cell. However, the fact that there is a decrease in cellular degeneration, and consequently, the fact that there is a preservation of the largest number of undamaged cells under the effect of protectors or of local anoxia, doubtlessly acts favorably on the state of hemopoiesis in the succeeding periods.

This amounts to the first piece of evidence of the weakening of the degree of the initial damage to bone marrow under the influence of protectors and of its role in achieving antiradiation protection.

Analogous results were obtained recently by N. P. Lebkov and A. N. Shevchenko [222] in experiments using protectors from a class of indolylalkylamines. During the investigation of a large group of analogs and homologs of tryptamine, they successfully disclosed a correlation between a decrease in the number of degenerating cells in the bone marrow and spleen and the protective action of the preparations. In effective compounds, for example γ-3-indolylpropylamine, generally did not influence the occurrence of radiation degeneration.

Mitotic activity in bone brain. Figure 6 represents the dynamics of change in mitotic activity of bone marrow in mice, subjected to X-ray irradiation in doses of 270, 400 and 700 rads under the conditions of the preliminary introduction of AET.

The standard mitotic index amounts to 1.17 ± 0.038%. In this case the proliferation of activity in the bone marrow of mice in the course of twenty-four hours does not change similarly as that in the cornea, epidermis, liver and other tissues [269, 270].

As can be seen from Fig. 6, over 2 h following irradiation the cellular division is almost completely suppressed, since the degree of its oppression is intensified with an increase in the dosage. The restoration of mitotic activity proceeds extremely slowly as

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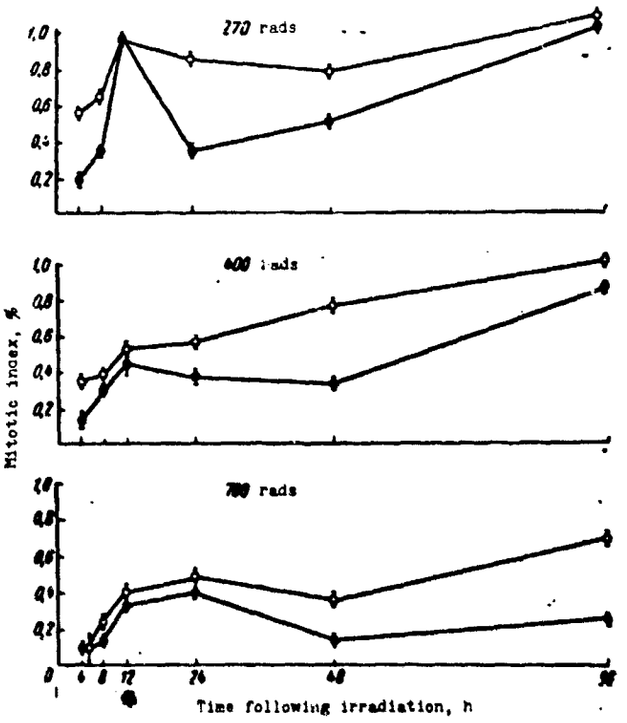

Fig. 6. Dynamics of mitotic activity in irradiated mice on bone marrow under the effect of AET (o) in comparison with a control (●).

well as with undulating variation, not attaining the original level even at the 4th twenty-four hour period with exposure. The preliminary introduction of AET facilitates the less expressed suppression of mitoses and its earlier activation.

The change in the mitotic activity during irradiation under conditions of local anoxia (Fig. 7) in principle cannot be distinguished from the results of experiments with AET; however, the absolute values of the mitotic index based on none other periods may be linked to the uncontrolled conditions of the experiment (experiments were conducted at an interval of 4 years). The first mitoses appeared over 9 h, since in bone marrow of the constricted extremity, the mitotic index reached the standard at the 2nd twenty-four hour period and then during the 10-12 days it exceeded the standard, but

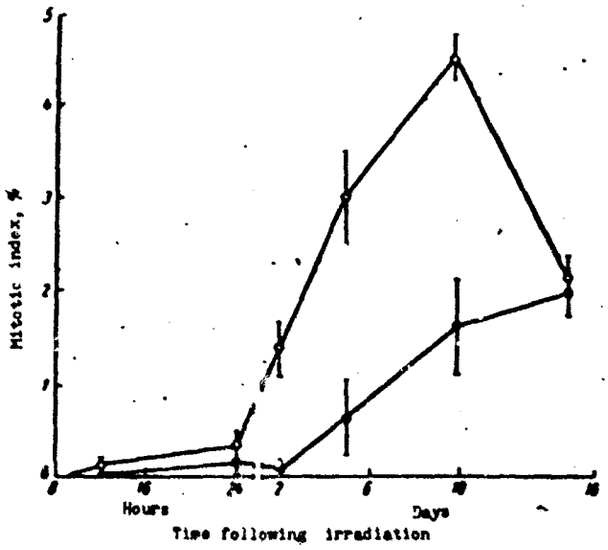

Fig. 7. Dynamics of mitotic activity on the bone marrow of mice, subjected to X-ray irradiation at a dose of 700 rads, under the effect of local anoxia. ● — control; ○ — experiment.

in the nonrestricted (control) the normalization occurred only during the period between the 5th and 10th twenty-four hour periods.

Thus, in animals protected by a protector or by the application of a tourniquet, the mitotic activity in the first 4-10 twenty-four hour periods following irradiation is almost 2 times higher, than in the controls. Consequently, even local asphyxia of the bone marrow, and chemical protection weaken the degree of radiation suppression of cellular division which does not act favorably on the rate of restoration of hemopoiesis.

This amounts to the second piece of evidence of role of reducing the initial radiation damage in achieving protection under the effect of modifying agents.

The intensification of cellular division in the bone marrow of irradiated mice under the effect of AET has been confirmed by N. F. Barakin and M. I. Yanushevskaya [224]; other researchers have

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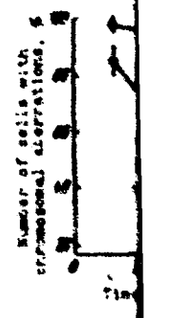

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observed this when using AEA [249], cysteine and hypothermia [271] and mexamine [268, 272].

Part interphasal cells may die as a result of structural damage of chromosones; this will be realized at the time of (or after) the division of the cell. In connection with this, it may be interesting to note the quantitative analysis of cells with chromosomal aberrations, induced by irradiation, and the effect of modifying agents on this process.

Structural damage of chromosomes. From the results of the cytological analysis of the bone marrow of mice, subjected to irradiation with the application of ligature on one of the thighs (Fig. 8), it is evident that in the constricted extremity, the number of cells with chromosomal aberrations is considerably less, than in the control, especially after 24 h, which somewhat facilitates their rapid elimination as a result of the more active division (see Fig. 7).

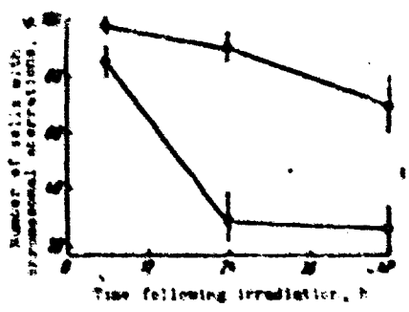

Fig. 8. Change in the number of cells with chromosomal aberrations in the bone marrow of mice, subjected to X-ray irradiation at a dose of 700 rads, under the effect of local anoxia: ● – control; o – experiment.

Figure 9 represents the dynamics of cells with chromosomal aberrations with X-ray irradiation of mice at doses of 270, 400 and 700 rads and its change under the influence of AET. For the intact animals it was noted to be 5 ± 1.4% cells with spontaneous aberrations of the chromosomal complex.

The number of cells with chromosomal aberrations increases with an increase in the absorbed dose. Between 8 and 48 h [illegible]

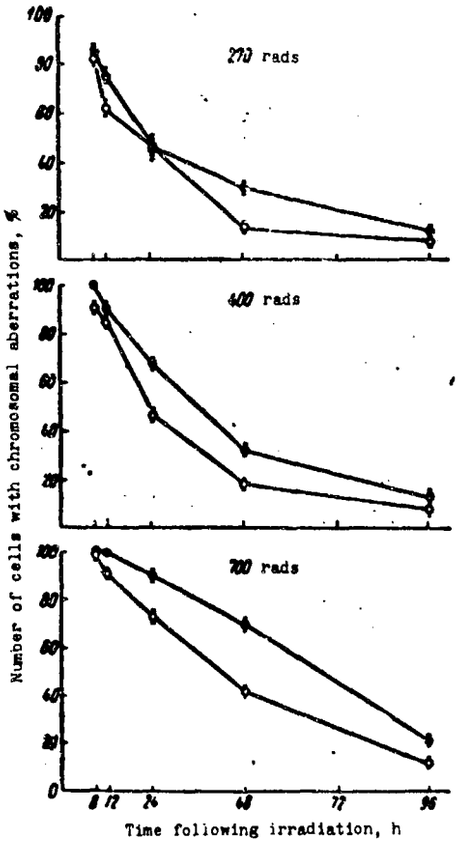

Fig. 9. Effect of AET on the dynamics of cells with chrom - somal aberrations in the bone marrow of irradiated mice: ● – control; o – experiment.

irradiation there is a steep drop in their number, well expressed at all doses of the protected animals, but even at the 4th twenty-four hour period the number of cells with aberrations still exceeds the standard.

The decrease in the number of cells of the bone marrow with structural damage to the chromosomes under the effect of AET or anoxia – the third piece of evidence of the weakening of the initial radiation injury of cells as bases of accelerated reparation, observed under conditions of antiradiation protection.

Analogous data on the reducing of the number of cells of the bone marrow of animals with induced radiation along with structural damage to the chromosomes were noted under the action of AET [224,

273], other thiol protectors [2 , 221, 223], general hypoxia [274], mexamine [268, 272], alanine and proline [275].

Thus, the protective agents reduce the number of hemopoietic cells, which perish as a result of the degenerative changes in the nuclear apparatus (soon after irradiation) or as a result of structural damage of chromosomes (relative to later periods), and likewise the time of suppression of the cellular division is shortened. All this creates definite cellular background for the protected animals, composing a source of subsequent regeneration [25] that obviously, should turn up during the immediate determination of the entire mass of cells.

Integral indexes of hemopoiesis. Hemopoiesis as a basic integral index has been very convenient for calculating the total number of nucleus-containing cells of the bone marrow (karyocytes) in the thigh of a mouse. As can be seen from Fig. 10, where the dynamics of karyocytes in mice is represented, protected by AET, at all doses, beginning with 2nd-3rd twenty-four hour periods after irradiation, the number of karyocytes exceeds the corresponding indexes in the control. The points, which reflect the action of doses 400 and 270 rads approximately coincide with the corresponding points, obtained in experiments on animals, protected at doses of 700 and 400 rads, respectively; therefore, it was possible to describe them in pairs of single curve (the difference, statistically, is doubtful).

Consequently, under the effect of the protector the known background of hemopoietic cells, governing the acceleration of the regenerative processes actually shows up. In the given experiments at all doses it comprises approximately 2 million cells in one thigh in comparison to the time of the maximum drop in their number (2nd-3rd twenty-four hour period following irradiation).

This amounts to the fourth piece of evidence for use in the consideration of the fact that the essence of the chemical protection in any case pertains to the decrease in the effective radiation dose

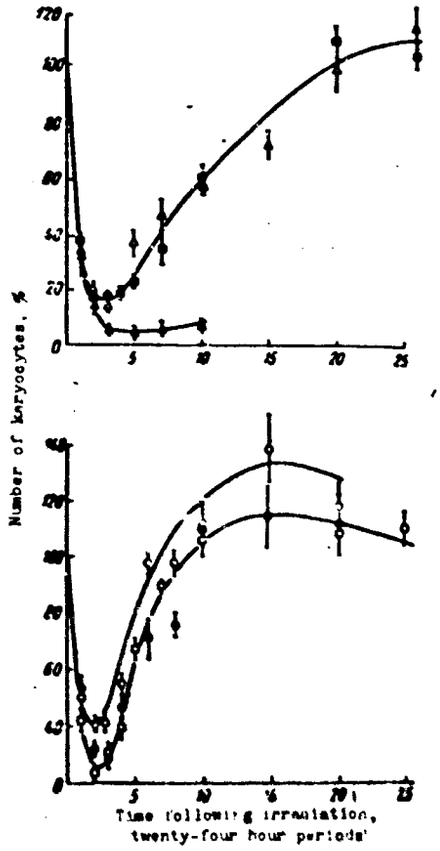

Fig. 10. Effect of AET on the change in the number of karyocytes in the bone marrow of mice depending on the radiation dose: ▲ – 700 rads; △ – AET + 700 rads; ● – 400 rads; ● – 270 rads; ○ – AET + 270 rads; □ – AET + 400 rads.

in association with the lowering of the level of the initial damage [255].

The [FUD] (ФУД) diminishing dose factor based on this criterion for AET is approximately 1.5.

Approximate data was obtained for AET during the analysis of the total number of cells of bone marrow in sections of the femoral bone [224], and likewise fore use in methods, analogous to ours [181].

Table 7 shows data about the effect of AET according to the weight of the spleens of irradiated mice. Unfortunately, this index reflects less accurately the essence of the process, first of all because of the large variations in the weight of the spleen for intact animals used as a standard. However, in the table it is

Table 7. Dynamics of the weight of spleens in irradiated mice under the effect of AET, mg.

Time following irradiation, twenty-four hour periods	700 rads		400 rads		270 rads	
	Control	Experiment	Control	Experiment	Control	Experiment
1	35 31—41	37 32—41	—	—	58 40—74	43 26—52
2	34 25—61	31 26—37	38 29—52	36 28—57	40 21—59	45 37—53
3	21 16—25	24 19—27	48 37—94	93 43—170	50 36—66	65 35—76
4—5	20 12—29	29 23—24	34 24—53	44 26—59	55 28—74	81 50—119
6—7	19 12—25	2. 21—41	—	118 62—129	70 38—138	76 44—141
10	31 16—51	61 35—90	65 32—123	137 71—250	65 47—90	80 61—128
15	58 26—65	150 108—196	138 94—164	238 110—596	—	—
20	—	149 100—250	170 92—218	157 88—349	—	—

Note. Mean data and ranges of fluctuations of 5-10 observations at each point; weight of the spleen as a standard is 88 (54-130) mg.

obvious that the drop in weight of the spleen of control mice during the first 2-3 twenty-four hour periods at all doses was almost equal and differed slightly from the corresponding indexes for protected animals. During the succeeding periods a difference based on doses makes itself felt and, furthermore, the weight of spleen in the experiment noticeably exceeds that of the control. Due to the wide range in fluctuations, the quantitative estimate of these data is hampered and, obviously, requires a considerable increase in the numbers of observations.

The controlled reducing of the initial damage of organs of hemopoiesis by the protector helps improve the indexes of peripheral blood in protected animals (Table 8) similar to that observed under the effect of [MEG] (МЭГ) mercaptoethylguanidine and AET in mice [276], rabbits [277] and dogs [278, 279].

Just as in experiments with local anoxia (see Fig. 3), the difference in the number of leucocytes is noticeable during the

Table 8. Change in the number of leucocytes in the blood of irradiated mice under the effect of AET, in thousands per 1 mm^3.

Time following irradiation	700 rads		400 rads		270 rads	
	Control	Experiment	Control	Experiment	Control	Experiment
3 w	10,5±1,4	—	8,1±0,9	—	8,6±0,7	—
7	16,1±1,2	—	14,6±1,1	—	10,6±1,3	—
12	7,7±1,1	—	9,1±0,8	—	8,4±0,8	—
1 day	2,9±0,4	—	4,9±0,5	—	5,6±0,6	—
2	—	—	3,1	4,4	6,1	6,5
—	—	—	1,4—5,4	1,5—8,5	3,6—8,8	4,1—12,1
3	0,6	1,4	—	1,9	2,4	3,7
—	0,5—0,7	0,9—2,0	—	1,1—2,4	1,6—3,1	2,6—5,3
4	—	—	2,05	—	2,9	3,7
—	—	—	1,6—3,2	—	1,5—3,7	3,1—5,4
5—6	0,7	1,8	1,41	6,0	4,1	7,5
—	0,4—1,1	0,9—2,2	7,5—3,0	5,1—7,2	2,5—5,9	6,8—9,6
8	—	—	—	—	6,4	9,3
—	—	—	—	—	4,5—9,7	6,1—14,1
10	0,4	3,7	1,2	7,2	4,8	8,5
—	0,2—0,5	2,0—4,1	0,6—1,6	6,0—10,0	4,0—5,2	6,0—16,1
15	—	—	7,3	8,8	8,19	9,9
—	—	—	4,4—14,0	5,6—12,2	7,4—8,6	7,5—10,9
20	—	9,3	12,1	11,7	—	—
—	—	4,0—13,6	8,4—17,5	9,0—15,3	—	—
25	—	10,9	10,0	13,8	—	—
—	—	8,0—17,0	8,0—13,2	9,4—16,0	—	—

Note. Mean data and ranges of fluctuations of 5-10 observations at a point; number of leucocytes as a standard 13.4 ± 6.49 thousands per 1 mm^3.

period of restoration. It was already mentioned that this, obviously, also served as a basis of a widespread point of view about the positive effect of protectors only on the restorative processes. Subsequently, with the development of quantitative methods of research on hemopoietic devices, many researchers changed their earlier views. Thus, specifically, this occurred in Langendorff's laboratory after the disclosure of the protective action of MEA and serotonin relative to the numbers of karyocytes in the bone marrow in the early periods following irradiation [184, 280]. Prior to Langendorff and Hagen based on the lack of difference in the decrease in the weight of the spleen and thymus during the first 2 twenty-four hour period following the irradiation of mice, protected by MEA, in comparison with the controls it was assumed that the protector only accelerates regeneration [234, 281]. As a matter of fact, according to [184, 280] the weight of the spleen and thymus of protected and control

mice during the first 2-3 twenty-four hour periods just as in our experiments (see Table 7) is not differentiated and does not always correlate with the dosage.

Correspondingly, they, themselves reexamined the previous results of researchers from Oak Ridge. Instead of presentations about the acceleration of regeneration [253, 242] under the effect of protectors, the same data was recently evaluated by them as a result of the reducing in the degree of radiation damage [181].

The Role of Individual Forms of Cellular Damage in the Mechanism of Radiation Injury and the Mechanism of Protection of Bone Marrow

The given data permits one to conclude that introduction of protectors into an animal, along with the creation of anoxemic conditions in the constricted section of bone marrow by the application of ligature to the extremity, helps reduce the arise of all types of cellular manifestations in the injury of bone marrow even if it should be transferred to a level, characteristic for the effect of a lesser radiation dose, with a corresponding increase in the survival of the animals.

Much evidence of the lowering of the initial damage in cells of radiation sensitive organs under the effect of protectors are received in the laboratory of E. Ya. Graevskiy, mostly in turn of an asserting point of view about the leading role of this phenomenon in the mechanism of antiradiation protection [23, 24, 240]. Aside from the data about the effect of protectors on radiation damage to bone marrow [224], in the same laboratory data are received about the reducing in the number of cells with aberrations and the degree of oppression of mitotic activity in the cornea under the effect of carbon monoxide [282], and in the small intestine under the influence of sodium nitrite [283] and AET [284].

Analogous results are also received by other researchers during the cytological analysis of bone marrow [32, 214, 221, 223, 268,

274, 275] and intestines [285-287]. Discrepancy in the data about the possibility of protection of the epithelium of the cornea by thiol protectors [288, 289] most likely is associated with the insignificant penetration of a protector in the cornea, especially in its central part.

The reducing of the initial radiation damage (in the form of the oppression of mitoses and the number of cells with chromosome rearrangements) under the effect of protectors was also detected in tumors [290, 291], in the culture of cells of animals [292] and in man [293] even in vegetative items [294-296] which proves the universality of this phenomenon for all levels of biological organization.

Returning to the system of hemopoiesis, one cannot help but note that, despite the large number of corresponding investigations, thus far the debatable question remains about relative merit of the separate forms of radiation injury of cells in bone marrow.

In accordance with most widespread point of view, the main contribution to this process involves the death of the cells during the interphase, even up to onset of cellular division which we have described as radiation degeneration [268, 272, 297-300]. The shown investigations are based only on a comparison of the percentage of the degenerating cells to the cells with chromosomal aberrations. During the comparison of data on the kinetics of devastation of the bone marrow of rats along with the number of aberrant cells, to the data about the periods of interphasal death, G. P. Gruzdev drew the conclusions that the aplasia of the bone marrow developing in the first twenty-four hour period was predominantly caused by the death of cells during the interphas [300].

The presented data itself allows for a more detailed discussion of this problem.

Most interesting during the examination time is the first twenty-four hour period after irradiation, during which there is a

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To get a presentation about the specific value of radiation degeneration, of inhibition of mitotic activity and of structural damage to chromosomes in the overall balance of radiation damage of cells of the bone marrow, it is necessary to compare their overall number and the number of cells with the mentioned forms of damage at defined moments of time.

Figure 11 presents calculated absolute number of degenerating cells in this manner at each given moment during a period of 0-24 h after irradiation at doses of 270, 400 and 700 rads.

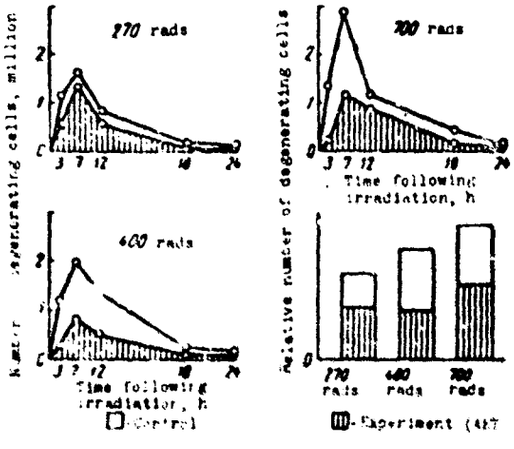


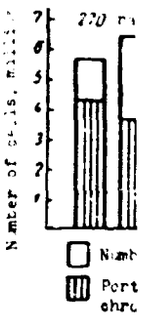
Fig. 11. Absolute number of degenerating cells in the bone marrow of mice during the first twenty-four hour period following irradiation.

By knowing the time, during which it is possible to observe the start of the degeneration of cells in the bone marrow, one would have to calculate the total amount of cells, which have decomposed over the first twenty-four hour period. However, to estimate the "life" time of the degenerated cell one must be careful. First

data about this are lacking in the literature. Recently it was disclosed that after the introduction of mexamine in the bone marrow of mice degenerating cells are also formed, which can be observed after 2 h. On this basis an assumption was made about the fact that the lifetime of any degenerating cell is also involved as a result of radiation injury and it amounts to 2 h [268]. Even if we take that lifetime of a degenerating cell which does not depend on the nature of the harmful agent, only then would it be possible to accept 2 h – the maximum period, during which it is possible to observe the perishing cell. The minimum time so far is impossible to determine. It turns out to be small as desired and over 2 h we will observe even more new perishing cells. Therefore, it is most expedient to limit oneself only to a relative comparison of the dependence of the number perishing during the interphase of cells over the first twenty-four hour period following the dose and application of the protector.

The results of corresponding calculations in the form of a diagram are presented in Fig. 11, from which it is clear that the number of cells, which were degenerating for the first seven twenty-four hour periods, increases with an increase in the dosage. If the sum of cells which have perished during the irradiation at a dose of 270 rads is assumed to be 1, then at 400 and 700 rads it will amount to 1.66 and 1.6 respectively. The introduction of AET before irradiation at all doses substantially diminishes the number of degenerating cells.

In an analogous way it is possible to calculate the absolute number of subdividing cells, and then, by knowing the portion of cells with chromosomal aberrations, one can also determine the absolute number of aberrant cells at each moment of time. If we assume the duration of mitosis is equal to 30 min [8], then one can planimetrically calculate the total number of sharing cells during the first twenty-four hour period, and among them, the number of cells having chromosomal aberrations. As can be seen from Fig. 12, which presents corresponding data, with an increase in the dose,



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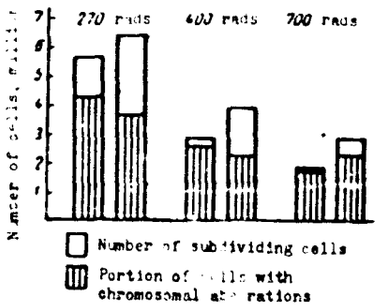


Fig. 12. The absolute number of subdividing and aberrant cells of the bone marrow during the first twenty-four hour period after irradiation. In each pair of columns the first – control, the second – experiment (AET).

the number of cells, which have subdivided over 24 h, is diminished, and the portion of aberrant ones increases: at 270 rads it amounts to 75, at 400 and 700 rads – 90 and 95%, respectively. Consequently, in the bone marrow during the first twenty-four hour period following irradiation an insignificant number of vital cells appears at all three doses: at doses 400 and 700 rads even in the protected animals it does not exceed $1.75 \cdot 10^6$ cells, but at 270 rads, $1.4 \cdot 10^6$ and $2.8 \cdot 10^6$ in the control and experiment respectively.

In the non-irradiated mice during this time 16.3×10^6 cells have subdivided; Consequently, in the analysis for causes of the devastation of bone marrow during the first twenty-four hour period it is possible to ignore the value of cellular reparation as a result of an almost complete suppression of the restorative processes.

Thus, over the given range of doses, only two factors basically have an effect on the quantitative composition of cellular population of bone marrow during the first twenty-four hour period following irradiation: early radiation degeneration, and continuing, as a standard, the discharge of cells in the bloodstream.

Even in the examination of Fig. 10 attention is drawn to the similar shape of the curve, reflecting the rate of devastation of the bone marrow during the first twenty-four hour period following irradiation at all doses. The independence of the change in the number of karyocytes can be expressed even more clearly from dose

and the utilization of the protector during the initial periods following irradiation on a semilogarithmic chart whereby it is represented in the form of exponents, along which all the experimental points lie (Fig. 13).

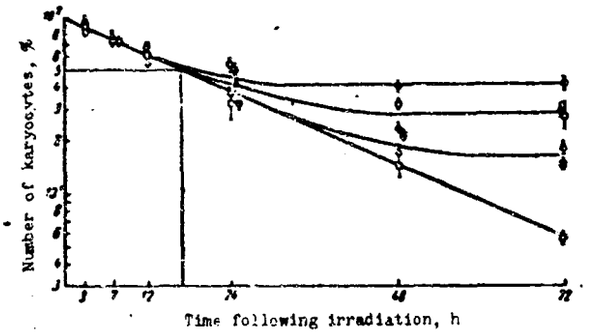


Fig. 13. Change in the number of karyocytes in the bone marrow of mice following irradiation at doses of 270 (○●), 400 (△▲) and 700 (□■) rads under the effect of AET: ●▲■ – experiment; ○△□ – control.

In the analysis of other works it is evident that at 12, 18 [181, 184] and 24 h [181, 184, 280] following irradiation, the degree of drop in the total amount of karyocytes in the bone marrow also depends on the dose, and statistically it cannot distinguish between the control and protected animals.

After 24 h (at 270 rads somewhat earlier) there is a breakdown in the shown linear dependence, since the time of deviation from the exponent increases with an increase in the dose, reflecting the difference in the reparative rate.

A similar rate of initial devastation of the bone marrow at different radiation doses indicates the independence of this process on some variables, which could substantially affect the number of cells. Such a variable value is the number of degenerating cells, which, as shown, increases with an increase in the doses, and diminishes under effect of the protector.

The entry of cells in the blood in normal non-irradiated animals exists in a dynamic equilibrium with the rate of cellular reparation as a consequence of which the quantitative composition of the cells of the bone marrow is put at the same level. Under the effect of irradiation this equilibrium is broken as a result of the suppression of mitotic activity and the breakdown of the nuclear apparatus of the cells. Then, it is logical to admit that the observed devastation of the cellular brain during the first twenty-four hour period, proceeding against a background of the almost complete absence of the reproduction of cells, can be determined predominantly by its continuing entry in the bloodstream where irradiation does not take place [137, 301, 302].

Absence of the effect of the radiation dose on the rate of disappearance of cells from the bone marrow, thyroid gland and spleen, independent to what Puck observed [185, 303], which further indicates the possibility of a complete simulation of the kinetics of radiation injury in the reproduction of cells by the introduction of inhibitors of mitoses kolqemida or vinblastina [303].

Our data, as well as Puck's results did not confirm that described by G. P. Gruzdev in the latent period (2-3 h), during which the content of myokaryocytes remains unchanged. This contradiction cannot be explained by obvious features of animals (the experiments of G. P. Gruzdev were made on rats), because in other investigations, performed together with A. L. Vygodskaya and L. Kh. Eidus [304], was also not noted a latent period during the irradiation of the rats by us. A number of karyocytes in the femur steadily fell during the earliest periods: through 1.5, 3 and 6 h following irradiation at a dose of 1000 rads it amounted to 80, 60 and 45% of the original level, respectively. Exactly the same data, independent of what we obtained was obtained by Ye. N. Kabakov and his coauthors [305], also not having been observed during the irradiation of the rats over the range of doses of 150-5000 rads in the latent period of devastation in the bone marrow. The latter passed into the early periods following irradiation to the same intensity, independent of the dose.

Ye. M. Kabakov and others explain the observable characteristic of devastation of the bone marrow in two ways: either by intensive disintegration of the cells, or by the continued entry of maturing cells in the blood without the completion of their diminution due to the oppression of division (it also allows for the joint participation of both factors).

The presented intrinsic data provide for no specific values of cellular disintegration during early devastation of the hemopoietic tissue. As was shown, the number of degenerating cells substantially increases with an increase in the doses; however, this does not happen at the rate of devastation. Consequently, despite the intensive cellular disintegration, it is possible to assume that the perishing cells are carried away "by the flow" to the periphery along with the remaining elements.

Also proof of this is one important fact. As can be seen from Fig. 13, at the highest of applied doses (700 rads) the rate of devastation remains constant for three days following irradiation, although the mass of cellular disintegration due to interphasal death is basically completed toward the end of the first twenty-four hour period (see Fig. 11). At the same time as can be seen from Fig. 6, proliferated activity at the 3rd twenty-four hour period is still sharply depressed which is also the basic reason for the continuing devastation of the bone marrow.

If irradiation does not occur at the rate of the entry of hemopoietic cells in the blood, then from the kinetics of the radiation devastation of the bone marrow it is possible to ascertain the rate of formation of the proliferated pool as a standard. Puck arrived at such a conclusion when comparing the reproductive ability of the cells of the bone marrow in vivo and in the culture of the tissue [185]. On the basis of these data he considers it possible to determine the rate of semirestoration of the marrow population, which amounts to 13 h for the studied line of mice. Using the same procedure, we calculated the time of semirestoration (semirejection

following irradiation) of the bone marrow, which in our experiments amounts to 17 h.

Thus, the leading cause for the initial devastation of bone marrow is the inhibition of cellular division and the breakdown in the quality of mitosis, and not the interphasal death of the cells.

A contradictory conclusion was made on the basis of a more intensive diminution of the cells in the bone marrow, rather than in the cornea of irradiated mice at doses of 150-750 rads, at a similar degree of suppression of mitoses and at an equal number of aberrant cells in both organs [306]. In connection with this it was asserted that the devastation of the bone marrow is determined by the early necrobiosis of the cells and does not depend on the breakdown of the processes of cellular division. However, the validity of such a conclusion is doubtful, since, except for given considerations, a constant elimination of the damaged and vital cells from bone marrow in this case is not considered, while in the cornea the offspring of vital cells remain at the site which also creates a difference in the degree of reduction in the overall number of cells. This observation to an equal degree is also related to the data by Puck, obtained on the culture of tissue [105], which likewise cannot be completely compared with bone marrow in vivo.

The conclusion made by us will not completely contradict the valid datum about the highest specific gravity of the interphasal death in comparison with the postmitotic death [268, 297-299]. Actually, the total amount of perishing cells during the interphase in the first twenty-four hour period always exceeds somewhat the number of cells with chromosomal aberrations. However, as a result of the delay of mitoses and of the continuing ejection of cells in the bloodstream the degenerating elements (outside of the dependence on its number) together with the unimpaired cells diminish to an equal degree and, consequently, are not able to substantially exert an effect on the kinetics of the devastation of the bone marrow.

A change in the total amount of karyocytes with time which reflects the rate of their ejection, retains its exponential character only up to the beginning of regeneration. The observed increase in the number of cells, then, proceeds at a varying rate, which increases with a decrease in the radiation dose or as a result of the utilization of a protector.

The different rate of growth of the cellular population depends on the differences in the rate of restoration of the mitotic activity in connection with the reduction in time of its inhibition on the protected animals, or in the less irradiated dose. This, in turn, provides for the start of reparation from a higher level. Furthermore, the quality of mitosis also acts on the amount of created cellular background, because even at a relatively high mitotic index, the presence of a large number of pathological mitoses hardly results in the formation of new cells.

For an example let us analyze the rate of growth of a population at a dose of 400 rads in control animals and under conditions of protection. As can be seen from Fig. 6, due to the higher mitotic index in the experimental animals, the restorative processes begin to manifest themselves earlier (from the 2nd twenty-four hour period), than in the control animals (from the 3rd twenty-four hour period). Therefore, the original number of cells, from which the growth of the composition of population in the protected mice begins, amounts to $7 \cdot 10^6$, and in the controls, $5 \cdot 10^6$ cells. The number of cells with chromosomal aberrations at the 2nd twenty-four hour period in the experimental animals amounts to 18%, in the controls on the 3rd twenty-four hour period, 22%. Consequently, the number of vital cells, i.e., the actual background, from which all subsequent reparation proceeds, amounts to $5.7 \cdot 10^6$ cells for protected animals, and $3.9 \cdot 10^6$ cells for controls, since in the latter it begins with a twenty-four hour delay.

As a result of the more rapid restoration of the mitotic activity and the lesser number of cells with aberrations in the protected

mice in comparison with the controls the completion of the proliferated pool is accelerated.

In 2nd-4th twenty-four hour period after irradiation, when a portion of cells with chromosomal aberrations is still rather high even in the experimental ones, as well as in the control animals, it is evident that the difference in the number of subdividing cells during this period is incomparably more than the difference in the number of aberrant cells (Table 9). Consequently, a reduction in the portion of cells with chromosomal damage under the effect of a protector can substantially affect the overall number of cells of the bone marrow.

Table 9. Change in the proliferated pool of bone marrow during 2nd-4th twenty-four hour period following irradiation.

Dose, rads	Number of subdividing cells, millions		
	whole	with aberrations	vital*
270	9,6	3,1	6,5
270 + 270	14,8	1,9	12,9
400	3,1	0,87	2,23
400 + 400	9	1,48	7,52
700	0,06	0,72	0,18
700 + 700	4	1,4	2,6

*There is an opinion that majority of cells with lethal aberrations perishes in the first mitosis.

Then it remains solely possible to explain the accelerated initial restoration of a proliferated pool in protected animals predominantly by weakening the degree of inhibition of mitoses under the effect of a protector.

As can be seen from Table 9, actually at doses of 270, 400 and 700 rads in protected animals during the period between the 2nd and 4th twenty-four hour periods following irradiation it forms 2, 4 and 15 times more vital cells, than in the control, respectively. Let us note that the number of forming cells at 270 and 400 rads

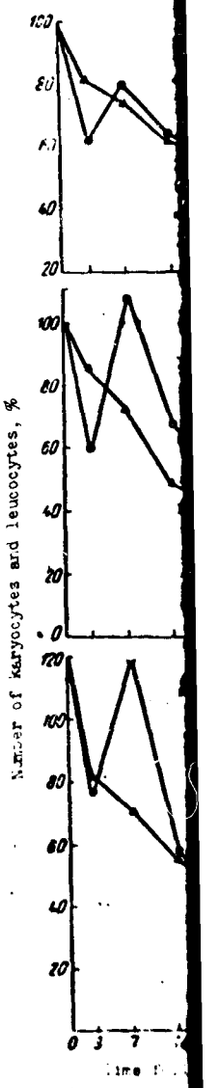
coincides approximately with that observed in the protected animals at 400 and 700 rads, respectively, i.e., FUD in this index for AET at both doses amounts to approximately 1.5, just as according to the criterion of survival [307].

It means in any case that neither the lowering of radiation degeneration nor the number of cells with chromosomal aberrations of the protected animals play any role in the outcome of acute radiation injury.

Obviously, not. On the contrary, in the bloodstream of protected animals the large number of unimpaired elements falls which governs the higher level of cellular composition of the blood, in a subsequent intensively completed introduction of new cells as a result of the blocking out of mitoses.

Figure 14 compares the data, reflecting the change in the number of karyocytes of the bone marrow with the number of leucocytes of peripheral blood in mice in the first 4 days following irradiation.

At all doses both curves coincide even from the first hours following irradiation. After 12 h, the number of leucocytes is reduced by 35-40%, and after 24 h – by 60-80%. Taking into account that the rate of ejection of karyocytes from bone marrow following irradiation does not change, one can assume that the reason for leucopenia during this time amounts to two circumstances: the diminution of cells due to their natural death (in the first place lymphocytes being most short-lived) and the incompletion by newly formed elements, since the degenerating cells, which are rapidly eliminated from the blood in different ways enter from the bone marrow in large quantities. Obviously, one of these ways – the mass phagocytosis, which occurs in the reticulo-endothelial system. It is very probable that of the observable animals in all forms the neutrophilic leucocytosis [248, 308] during the initial hours following irradiation is caused not by the simple redistributive reaction [308], but caused by the need for the mobilization of



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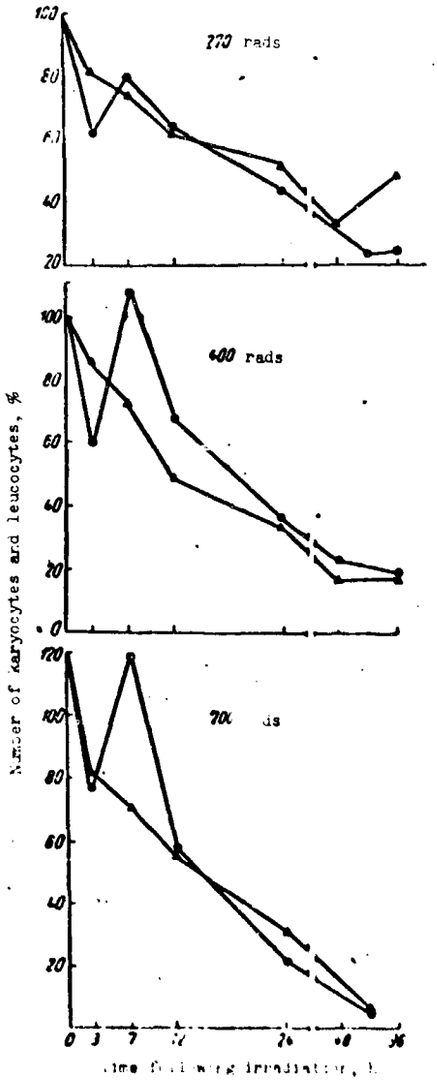

Fig. 14. Dynamics of the number of karyocytes (▲) of the bone marrow and leucocytes (●) of the peripheral blood of irradiated mice.

neutrophilic reserves from the depot and by accelerated maturing of granulocytes [315], since during this time a large quantity of cellular detritus should accumulate in the blood.

As can be seen from Fig. 14, leukocytosis was observed even in our experiments, coinciding in time with the maximum degeneration in the bone marrow (4-6 h following irradiation). The mass phagocytosis proceeds in the bone marrow [309-312], manifesting even during the first minutes and hours following irradiation. Evidence of this is

the formation of identifiable micronecrosis by luminescent microscopy by means of which the macrophagic nature was recently disclosed [313, 314]. It is probable, therefore in smears of blood of the mammals the degenerating cells cannot be successfully detected [315], although they doubtlessly enter in large quantities from hemopoiesis organs, but, according to expressed assumptions, are immediately picked from the bloodstream by reticular cells of parenchymal organs. Of interest in this plan are the data on the activation of phagocytotic action in the initial hours following irradiation [316-318], for which until now no acceptable explanation has been found.

Toward the end of the 1st twenty-four hour period the cleansing of degenerating cells from the organism basically ends and quantitative composition of peripheral blood should reflect the number of vital cells. As can be seen from Fig. 14, at doses of 270, 400 and 700 rads the number of leucocytes amounts to 45, 35 and 20% of the original, respectively.

It is clear that the magnitude of leucopenia during this period is determined predominantly by the degree of cellular destruction due to interphasal death. Subsequent redoubling of leucopenia can be explained by the fact that the mitotic activity of the bone marrow long since remains at a low level (in this case, a considerable number of mitoses due to the damage of the chromosomal complex leading to the formation of new cells), but the natural diminution of the declining formal elements continues at the same rate.

As a result of the setting off of mitotic activity and the elimination of all aberrant cells gradually the balance of the forming of new elements with those existing in the bloodstream is restored, since the periods of normalization are lengthened with an increase in the dose of irradiation.

Thus, the depth and duration of leucopenia, and subsequently, the outcome of the acute radiation syndrome in contrast with the kinetics of the initial devastation of bone marrow are determined

primarily by the mass interphasal death of cells, by redoubling new elements in the subsequent retarded formation and by the structural injury of the chromosomal complex.

With a decrease in the radiation dose or as a result of the utilization of protective means the degree of all the enumerated types of damage is reduced. This facilitates the reducing of the degree and the shortening of the duration of leucopenia and it determines the favorable outcome of injury.

By evaluating role of the separate forms of cellular damage in the mechanism of radiation injury of the bone marrow, specific attention should be focused on the duration of the retardation of cellular division. The acceleration of the blocking of mitoses should inevitably lead to an increase in the sizes of the cellular background, from which regeneration begins, and should facilitate its more rapid normalization. If this were valid, then a new trend would be found for sought-for preparations, which could be effective not only upon being introduced into organism prior to irradiation, but also as a means of early therapeutics of the radiation syndrome at moderately lethal doses.

According to the data L. B. Berlin [319], cystamine itself after certain short-time and insignificant suppression of mitotic activity of the cornea and intestine of intact rats causes a sharp increase in subsequent several twenty-four hour periods. Obviously, the effect of the initial retardation of mitoses, noted under the effect of cystamine and for bone marrow [320], does not render its protective effect as a result of independence of the rate of destruction of the bone marrow in the 1st twenty-four hour period, and subsequent activation of cellular division from a higher level can play a substantial role in the acceleration of the restorative processes.

Furthermore, judging from the weakening of the initial radiation suppression of mitoses in the protected animals, it is possible

propose that the shown antimitotic action of cystamine [320] overlaps with its effect of weakening the dose.

Thus far, this was not given attention, because experiments, as a rule, were conducted under conditions of absolute lethal doses, when any interferences following exposure may not be effective because of the fact that the majority of the cellular elements hardly exert an effect opposite to injury.

There is every reason to believe that among them, in the arsenal of already tested means, which are slightly effective at absolute lethal doses, preparations can be made, selectively so, which can affect mitotic activity. Obviously, one ought to turn to an estimate from these positions of possibilities for utilizing a certain neurotropic combination. As an example it is possible to isolate the effect of strychnine [321, 322], securinine [323], as well as rezerpina. The effect of the latter was erroneously associated with the releasing of serotonin [324-326], since the maximum effectiveness reserpine can be observed over 24 h, whereas due to serotonin, a trace doesn't remain.

Without exception, also, is the fact that the activation of mitoses is associated with the effect of the various preventive agents (pestle of glass, vaccine preparations, to testosterone and many other means), effective upon introduction over 10-14 days prior to irradiation.

By not incorporating such a mechanism of protection by the indicated means, we consider it expedient to conduct the corresponding experiments, taking into account not only the theoretical side of the problem, but also its practical aspect.

In this connection it is appropriate to call to mind the investigations, in which the favorable effect of MEA [69, 327-329] and serotonin [326] was detected upon the introduction of the latter not only to irradiation, but also after it. We will still return

to the analysis of the shown works during the discussion of the problem postradiation restoration and during the practical aspects of protection.

In conclusion it is necessary to emphasize that the developed views bear only structural pattern. The need for conducting a detailed hematological analysis as well as the pursuance of research on other forms of animals exists. Their results can introduce corrections in the given positions.

One should first evaluate quantitatively the value for the reparation of the accelerated maturing of the cells, the shortening of the separate stages of the mitotic cycle [333], and likewise, should study the characteristics of injury and protection of separate outgrowths of hemopoiesis. However, we are faced with the basic fundamental positions which in this case should not substantially change.

Conclusion

As a result of the quantitative analysis of injury and protection in bone marrow and the differentiated estimation of the role of radiation degeneration of cells (interphasal death) in this process, structural damages of the chromosomal complex (chromosomal aberrations) and retardation of cellular division, it is possible to draw the following conclusion.

The leading component of radiation devastation in bone marrow, and according to published data and lymphoid organs, during the 1st twenty-four hour period following irradiation there is a delay of cellular division and a continuing ejection of the formal elements in the bloodstream.

Interphasal death and chromosomal injuries of cells have [illegible] effect on the initial rate of devastation of bone marrow, but they determine the subsequent outcome of radiation injury, i.e. the development of irradiated [illegible].

The protective action of protectors consists of the weakening of all types of initial radiation damage to cells, being manifest at the beginning of regeneration, which in protected animals is facilitated by the formed background of vital hemopoiesis cells. The size of this background is determined by the degree of weakening of the initial radiation injuries to the cells, by the quantitative expression of which is the amount of FUD of an actual protector.

Protection of the cells of bone marrow has been well expressed at all doses, leading to the injury of hemopoiesis, including sub-lethal doses. In connection with this the data on the sharp drop and even in effective protection with fractionated irradiation are not properly understood.

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ANTIRADIATION PROTECTION WITH FRACTIONATED IRRADIATION

From the vast number of investigations in the field of chemical protection only individual ones and those with discrepant results have been completed under conditions of fractionated irradiation.

Beginning with the first publication in this direction, in which Rugh and Clugston [334] showed the complexity of radiation injury in mice under the effect of β-mercaptoethylamine [MEA] (МЭА) with daily irradiation at a dose of 100 R, a reduction of the protective effect with repeated irradiation was noted repeatedly. Langendorff and Catsch [335] in their research on the effect of MEA under conditions of double irradiation in doses of 175-500 rads with an interval of 24 h, and Noble with coauthors [336] – under conditions of repeated irradiation in doses of 50-200 rads using aminoethylisothiuronium [AET] (АЭТ) arrived at such a conclusion.

Mewissen [337] with triple irradiation of mice at intervals of 5 twenty-four hour periods in doses of 300-740 R observed an increase in the lethal dose [$LD_{50/30}$] ($ЛД_{50/30}$) under the effect of cystamine with 416 to 597 R, and under the effect of MEA with 416 to 700 R [337a]. The author did not consider that the less effectiveness due to cystamine could have been caused by the short interval of time between his oral introduction and the irradiation (20 min).

S. N. Aleksandrov and K. F. Galkovskay [338-340], observing a lack in effectiveness of MEA with quadruple irradiation of mice at a dose of 200 R with 7-day intervals or its reduction with repeated

irradiation at doses of 200 and 500-600 rads, this is explained by the appearance of a reduction of the ability with the first irradiation of biopolimerov to connect to the protector, as a consequence of which they are less protected from the inactivating effect of oxygen with the subsequent radiation exposure.

The assumption about a change in the reactivity of the organism to the protector following preliminary irradiation as a means of reducing the protective effect has been also expressed by other researchers [238, 341]. Without any explanation whatsoever P. P. Saksonov and coworkers [342] asserted that there was a decrease in the protective features among a number of protectors in diverse variants of fractionated irradiation. We also arrived at such a conclusion proceeding from out first experiments using aminothiols and indolylalkylamines at the 2nd, 4th and 8th fold irradiation of mice [6].

The very scant information on this problem is confirmed by the shown works. In this case, a part of the research has been published only very recently. It is completely obvious that little has been developed in this aspect of protection. Amid the research an explanation goes beyond the limits of academic interests, if we take into account the restraints for the means of the practical utilization of protectors with radial therapeutics [6, 7] and other possible aspects of utilizing the protective means under conditions of the repeated irradiations.

The investigations themselves are conducted from a viewing angle of a further clarification of the role of weakening the initial damage to the bone marrow in the realization of the chemical protection with fractionated irradiation.

Work done in this direction requires the acquisition of information about the behavior of protectors in an organism, about the protection of separate parts of its systems, about the dynamics of injury and about restorative processes depending on the conditions

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of the experiment (radiation doses, numbers of introduced protectors, intervals between separate irradiations, and others).

In literature there is only limited information, predominantly related to the distribution of protectors under conditions of single irradiation in fatal doses.

Presented below are the results of the first investigations, conducted in this direction of rather elucidated essence of the considered phenomenon.

Behavior of Protectors in an Organism of Irradiated Animals

One of the proposed studies on the research of the problems is a clarification of dependence of the protective effect on the amount of the introduced preparation and radiation dose. First of all, this is important in connection with the data about the increase in the toxicity of preparations of irradiated animals [14, 181] and the possible change in the reactivity of the irradiated organism [238, 338-341]. Individual works along this line were made under conditions of single exposure [18, 343], and they do not provide a basis for extrapolating their data to the results of the fractionated irradiation.

In preliminary investigations we conducted a study of the change in the protective effect with a simultaneous reducing in the number of preparations and of a single radiation dose [6]. Results of these experiments made it possible to draw the conclusion that with a simultaneous and an equal (by 2 times) reduction in the single radiation dose (2-4 fold exposure) the amount of protector of the protective effect of AET and mexamine is also weakened, and MEA disappears.

Consequently, between content of the protector in the organism and the amount of absorbed dose under conditions of repeated irradiation direct quantitative relationships are lacking.

Published information along this line is ambiguous. For some protectors at the same radiation dose, the effectiveness is intensified with an increase in its amount. The degree of protective action of cysteine, for example, increases linearly as the logarithm of its number [18]. At a constant (optimum) amount of introduced MEA and AET, the protective effect diminishes with an increase in the dose of irradiation. Proportional relationships between the protective effect and the introduced amount of the compound are shown for MEG [343, 344], AET and aminopropylisothiuronium [APT] (АПТ) [181].

However, for other compounds contradictory data have been obtained. The maximum protective effect of amphetamine [20] and serotonin [14] in mice is observed only at their optimum amounts, the increase of which already results in a sensitizing effect.

Protective effect of aminopropylmethylisothiuronium [APMT] (АПМТ) with an increase in the introduced amount at first increases, and then, despite its 4-fold increase, it does not change [181].

The results of our experiments [6] will also contradict concurrent controversial hypothesis, and the hypothesis of mixed disulfide, because, based on these presentations, one should expect retention of the protective effect with the simultaneous reduction in the amount of introduced compound and the dose of radiation. As it turned out, such a parallelism for the tested protectors, primarily for MEA, was not observed. From these positions, consequently, it is impossible to explain the reduction of the protective features of the preparations with fractionated irradiation, since if one deals only with the concurrent ratio between the molecules of the protector and the energy of radiation, then protective effect would be completely manifested. However, for such a conclusion it is necessary to have information on the behavior of protectors in an organism depending on their amount and condition of irradiation.

Distribution of S^{35}-AET Depending on Its Amount in Intact Animals

The distribution of S^{35}-AET or mercaptoethylguanidine [S^{35}-MEG] (S^{35}-МЭГ) in an organism of intact animals has been studied by many researchers, using methods of radiometry [155, 345-351], chromatographic analysis [352, 353] and autoradiography [354, 355].

The shown investigations, having varied and independent goals (dependence of the distribution on the means of introduction, the balance of bound and free S^{35}, analysis of chemical forms and the bond of protectors, dynamics of their behavior in the organism, and others), were conducted only from one, as a rule, optimum dose of protector. They confirmed the original information [155] about the selective distribution of AET with a preferential concentration in the liver, spleen, bone marrow and mucous intestine and less so in the muscles, blood, brain and testicle. In connection with this, in the research on the distribution of AET depending on the quantity we introduced, only separate organs were used: liver, spleen, blood and brain. By limiting the time of radiometric analysis to 30 min following the injection of S^{35}-AET, we calculated that the quantity of measurable radioactivity predominantly reflects the content of the whole molecule of preparation in accordance with the results of the determination of the SH-grupp [356] and of special chromatographic investigations [352, 353].

As can be seen from Table 10, the introduction of AET in doses, differing from the optimum by 2 and 8 times, did not substantially effect the relative distribution of the preparation throughout the organs. The quantity of specific activity (4.8 or 20 μCi per mouse) on the distribution was not stated; existing differences were statistically unauthenticated.

Let us note that the induced disorders of hemodynamics [357, 358] by "protective" numbers of AET, apparently, are not eliminated even at such a reduction in quantity of introduced preparation.

Table 10. Distribution of S^{35} per 1 g of tissue over 30 min following subcutaneous introduction, %.

Number of introduced AET, mg/kg	Specific activity, μCi/mouse	Blood		Brain		Muscle		Spleen	
		No. of mice	$M \pm m$	No. of mice	$M \pm m$	No. of mice	$M \pm m$	No. of mice	$M \pm m$
150	4,8	6	51±6	6	51±5	6	178±15	6	109±9
	20,0	6	50±5	6	66±5	6	231±23	6	169±19
75	4,8	6	41±1	8	45±3	7	166±12	8	114±10
	20,0	7	59±9	7	64±9	6	226±18	6	173±24
18,75	4,8	10	37±1	10	59±3	16	156± 5	9	102±5
	20,0	6	41±4	6	41±3	6	181±16	6	141±17

Note. M – average value, m – quadratic error.

The obtained results are in accordance with the data about the fact that a 200-fold change in the concentration of MEG did not affect the amount associated with the proteins of plasma of a combination, which after the establishment of equilibrium is equal to 0.5-1% of the introduced dose [181].

The research on the dynamics of the inflowing AET in the organs was explained by the fact that its concentration in the blood attains a maximum even in the first 2.5 min. In the liver this maximum is shifted to 10 min and according to the absolute value it exceeds by 5 times the concentration in the blood. At 30 min the concentration of the protector in the organs begins to dimish, which on the whole, coincides with the optimum time of manifestation of the protective effect (Fig. 15).

Other regularities, not noted earlier, were detected in the brain. As can be seen from Fig. 15, the accumulation of the preparation in the tissue of the brain proceeds gradually, attaining a maximum within the limits of observable periods only at 30 min.

Most interesting is the fact that with the onset of death over a 7-10 min period following the introduction of clearly defined toxic dose of preparation (300 mg/kg) the content of AET in the tissue of the brain was 2-4 times less, than following the injection of transferable doses (100 and 150 mg/kg). On this basis, in spite of the

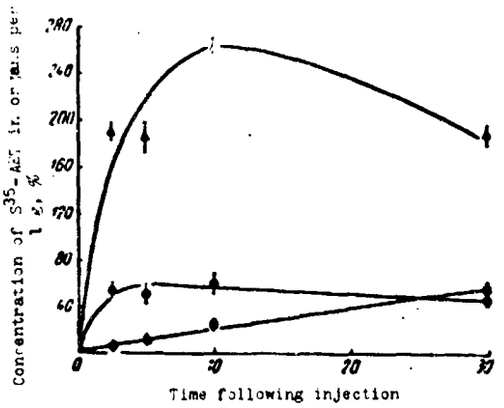

Fig. 15. Dynamics of inflowing S^{35}-AET in muscles (▲), blood (●) and brain (■) of intact mice upon intraperitoneal introduction.

widespread opinion about the central mechanism of death due to the toxicity of AET, an assumption was expressed that the latter has a predominantly peripheral nature, in all cases not associated with the immediate effect of the protector on the central system [359].[1]

Absolute content of AET in the liver over 10 and 30 min following injection correlates with the introduced quantity in the organism (Fig. 16), since the concentration of the protector with subcutaneous and intraperitoneal introduction at the same amount over 30 min does not differ.

[1]Recently we were given the opportunity to acquaint ourselves with the work of Born, Timofeyeva-Resovskaya and Wolf, carried out in 1943. The authors studied the distribution of radioactive manganese for the purpose of research on manganic poisoning. It was explained that in contrast with the distribution in the internal organs, the accumulation of isotope in the brain proceeds gradually, constantly increasing during the whole period of observation (6 h), since the sum total amount in the tissue of the brain was 10-20 times less than in other organs.

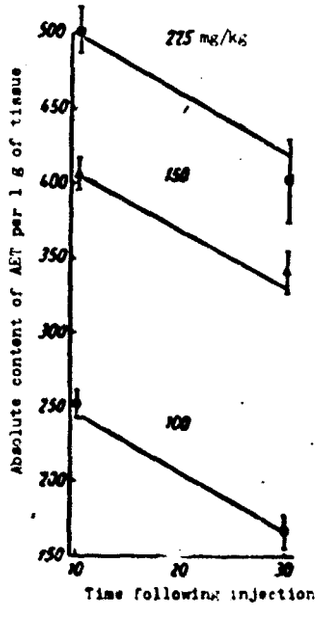

Fig. 16. Content of AET (μg) in the liver tissue of intact mice upon intraperitoneal introduction in different quantities [137, 359].

Distribution of S^{35}-AET in Irradiated Animals

As can be seen from Table 11, the content of protector in organs immediately after a single exposure, with the exception of the liver, does not differ from the control. In the liver it is steadfastly lowered by 20%. Subsequently the effect of irradiation, which leads to, obviously, the retardation of AET in the tissues, should follow from the steadfast increase in its content throughout the organs (again – except for the liver) upon the introduction immediately following the irradiation and its determination over 20 min. Possibly, the mentioned intensification of the toxicity of protectors for irradiated animals [14, 181] can be explained partially in this way.

The increase in the concentration of S^{35}-AET in the organs of irradiated mice and rats in the first hour following radiation exposure is confirmed by the subsequent works of A. M. Rusanov and coworkers [346].

Table 11. Distribution of S^{35} per 1 g of tissue upon the intraperitoneal introduction of 150 mg/kg of AET depending on the time of irradiation at a dose of 800 rads, %.

Tissue	Over 20 min following injection of an intact animal		Injection of AET for 5 min prior to irradiation, radiometry immediately following irradiation				Injection of AET immediately after irradiation, radiometry over 20 min following injection			
	n	$M \pm m$	n	$M \pm m$	t	p	n	$M \pm m$	t	p
Blood	18	48.9±1.8	17	49.5±3.0	0.2	>0.5	18	67.5±3.8	4.5	<0.001
Brain	12	34.7±1.8	12	38.5±1.0	1.8	>0.05	12	45.4±2.3	3.6	<0.01
Spleen	7*	106.5±5.1	7*	140.5±6.2	4.37	<0.5	7**	141.3±4.4	5.7	<0.001
Liver	18	236.2±9.9	18	181.8±5.2	4.1	<0.01	18	210.6±12.2	1.9	>0.1
Testicles	5***	47.7±4.5	6***	41.8±3.9	1.0	>0.3	6***	88.5±3.7	3.7	<0.01

Note. n – number of observations, t, p – exponents of the degree of reliability with respect to the corresponding datum for intact mice.

*Target from two spleens.

**Target from four spleens.

***Target from four testicles.

The utilization of AET with fractionated irradiation was accompanied by a short-time increase in the concentration of the preparation in an organism with normalization over 20 min (Table 12); moreover the distribution of AET in the liver also did not correspond to the change in the concentration in blood. Without exception, this is the manifestation observable following irradiation of the breakdown of hemodynamics [360] in the system of the vena porta [359].

Our assumption about the breakdown of the blood supply of the liver [359] was subsequently confirmed by other researchers in direct experiments. With a local irradiation at a dose of 1000 R, the blood supply of the organ was diminished by 20% [361], i.e., by approximately the same amount as that in our experiments [359].

The results of conducted experiments allowed us to draw the conclusion that the weakening of the protective effect of AET during the fractionated irradiation was a simultaneous decrease in the quantity

Table 12. Distribution of S^{35} per 1 g of tissue upon intraperitoneal introduction of 150 mg/kg of AET under conditions of triple irradiation at a dose of 400 R at intervals of 72 h, %.

Tissue	Over 20 min following injection of an intact animal (control)		Injection of AET for 5 min prior to each irradiation, radiometry immediately following the termination of the last irradiation				Injection of AET for 5 min prior to each irradiation, radiometry over 20 min following the termination of the last irradiation			
	n	M ± m	n	M ± m	t	p	n	M ± m	t	p
Blood.....	18	48.9±1.8	10	57.0±2.8	2.4	<0.05	12*	48.0±1.6	4.8	<0.01
Spleen.....	7*	146.5±5.1	4**	164.6±11.3	4.7	<0.01	9	119.7±8.4	1.3	>0.1
Liver.....	18	226.7±9.9	9	265.0±9.0	1.0	>0.1	11	191.9±8.2	2.7	<0.005

Note. Designations are the same as in Table 11.

of introduced protector and radiation doses is associated with the change in the distribution of the preparation in the organism. One can only admit that the irradiation, resulting in a certain retardation of a protector in the tissues, facilitates the intensification of its toxicity.

It is not inadvertently that to avoid the death of the irradiated annimals due to toxic effect of the protector, it is recommended to reduce the quantity of the latter by 10% in comparison with the quantity, introduced into intact animals [181].

The Effect of Protectors During the Irradiation at Sublethal Doses

With fractionated irradiation single doses are relatively small; therefore, the degree of manifestation of protective effect of protectors under conditions of irradiation at sublethal doses must be explained. This problem itself amounts to an important and unsettled part of the problem of chemical protection of an organism.

According to some data, the amount of the diminishing dose factor [FUD] (ФУД) does not change over a significant range of doses. This was shown by the relationship of cysteine [18, 36],

AET [307, 362], MEG [364], hypoxia [365], mexamine [307, 365], cystaphos [307]. In the others, in the example of MEA [366] and AET [366, 367] a certain decrease in FUD with the lowering of the dose of irradiation was shown.

The conclusion about weakening of protective features of protectors with the lowering of the radiation dose is made also on the basis of the observed decrease, in this case, in the coefficient of protection [177, 238], index of survival [179] and magnitude of difference between the survival of the experimental and control animals [368].

Data about the complete absence of protection [293, 369-371] as well as about loading of radiation injury under the effect of using protectors during irradiation at weak or moderately lethal doses [177] represent an extreme expression of these views.

In the elementary statistical analysis of the data from E. N. Antipenko [370] it is evident that they are unreliable, because even within the limits of less than two errors, contradictory conclusions can also be made directly, namely: FUD at 500 and 300 R or even higher at 700 R [177].

Even less reliable ($R > 0.05$) are the conclusions about the decrease in the effectiveness of allylnorantifeina [368]. In the work of Koch and Langendorf [179] the index of survival with its characteristic deficiencies is used. Treatment of the same data, produced by V. I. Suslikov with a calculation of the coefficient of protection [177], showed that the latter even increases monotonically during the shift from 810 to 690 R. Attempts of a quantitative analysis of the effect of AET on cellular reparative processes at different radiation doses and in this case, the drawn conclusion about the decrease in the protection with a lowering of the radiation dose to 900 and 100 R [371] have also been unconvincing, since the utilization of AET in this instance hardly becomes a protective effect (100% survival) even during irradiation at a lethal dose of 100 R.

This, paradoxical phenomenon, at first sight, attempts to explain the different protection of defined systems, to an unequal degree of injurious radiation at various doses [177, 179, 369], by endocrine effects [367], by immune reactions [238] and, finally, by the toxicity of protectors, especially being manifested with weakly expressed radiation injury [177].

Below, the results of their experiments pertaining to the problem are given.

Protective Effect with Single Irradiation

Using the survival of animals as criterion of protection during the irradiation at moderately lethal doses requires a large number of observations and repeated experiments, and during the irradiation at sublethal doses, based on intelligible reasoning, the utilization of this criterion is generally infeasible. Therefore, one is faced with entirely justified quantitative research on the injury of bone marrow, which determines, as indicated, the outcome of acute radiation sickness during the irradiation at doses of 150-900 rads.

With this aim we studied the change in the number of karyocytes in the femur of a mouse during irradiation at doses of 150, 300, 450, 600 and 900 rads under the influence of various protectors in 3 twenty-four hour periods after irradiation, when greatest aplasia of the bone marrow is observed (see Fig. 10). As can be seen from Fig. 17, protective effect is clearly expressed at all radiation doses. The FUD based on this criterion over the range of doses of 300-600 rads is approximately equal and amounts to 1.5 and 2 for cystaphos and mexamine, respectively, but at a dose of 900 rads, which exceeds the absolute lethal, it is reduced. In examining the chart it is evident that the difference in the number of karyocytes, in the experimental and control animals at all doses amounts to $2 \cdot 10^6$-$3 \cdot 10^6$ cells for cystaphos, as noted earlier for AET, and $4 \cdot 10^6$-$6 \cdot 10^6$ cells for mexamine. Thus, the experimental confirmations were obtained of the earlier expressed hypothesis about the potential ability of a protector to shield determined number of

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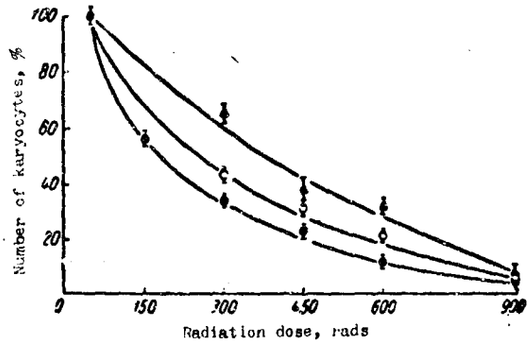

Fig. 17. Change in the number of cells of the bone marrow in the femoral bone of mice on 3rd twenty-four hour period after irradiation at different doses under the effect of protectors: ● – control; ○ – cystaphos; ▲ – mexamine.

cells, creating a known background [25], a portion of which on the whole balance of preserved elements of the bone marrow, and consequently, relative value also diminishes with a reduction in the dose. This is quite obvious in the comparison of the ratio:

$$K = \frac{a-b}{a},$$

where K – the portion of protected cells as the entire amount being preserved at the given dose of irradiation; a – total number of vital cells in the experiment; b – total number of vital cells in the control.

A much clearer created situation is represented in the diagram, shown in Fig. 18.

Number of injured cells statistically increases with an increase in the dose, and the protected ones always seems definite in their number; therefore, in proportion to the decrease in the dose on the lowering of the value K even that which is a part of the protected cells will also appear without injury or injured nonlethally.[1]

[1]By the number of injured cells, the resulting injury to all types of cells, described in Chapter III, is implied.

As can be seen from Fig. 18, during the transition from a minimum absolute lethal dose [$MALD_{100}$] ($МАЛД_{100}$)* to LD_{20}, K it diminishes from 1 to 0.07.

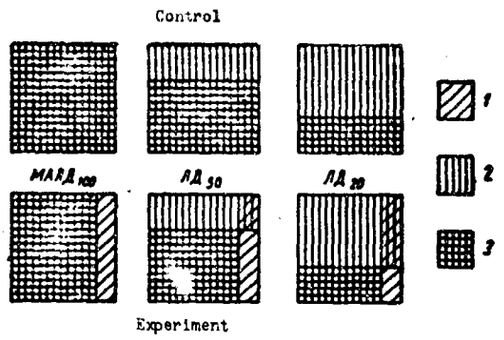

Fig. 18. Degree of manifestation of the protective effect of protectors at different radiation doses (diagram): 1 – protected cells; 2 – noninjured; 3 – injured.

Thus, the lowering of the coefficient of protection in survival with a decrease in the radiation dose is easy to explain, although the absolute amount of protective activity of the protector in relation to the capability of protection of bone marrow does not change. Under these conditions, consequently, the protective features of preparations are not lost, but are masked. In other words, at sublethal doses one would create "disadvantageous" conditions for the exposure of portions of the protected cells in the overall balance of vital cells, because the probability of protection is lowered which also manifests itself in the relative lowering of the increase in survival.

In Table 13 actual amounts of FUD and K, calculated according to the data given in Fig. 17 are shown.

*[Translator's note: $МАЛД_{100}$ is not definable in available source material. It is possibly a lethal dose level, as ascertained by the International Agency of Atomic Energy (MAFATE)].

Table 13. Degree of protection of bone marrow on the 3rd twenty-four hour period following irradiation.

Dose, rads	Protector	FUD	K	Dose, rads	Protector	FUD	K
300	Cystaphos..	1.4	0.23	600	Cystaphos..	1.5	0.48
	Mexamine...	2.0	0.32		Mexamine...	2.0	0.65
450	Cystaphos..	1.4	0.26	900	Cystaphos..	1.3	0.33
	Mexamine...	1.9	0.39		Mexamine...	1.4	0.50

As seen, over the range of doses of 300-600 rads along with constant FUD for each one of the protectors, the amount of *K* is reduced with a decrease in the dose. At lesser doses, the exposure of the protective effect of the protectors is not possible because of the character of this method of statistical variability which exceeds the evaluated differences, and likewise in connection with the sharply diminishing quantity of *K* in proportion to the further lowering of the dosage. At doses of 50 rads and less, the change in the number of karyocytes cannot be determined [185].

Protective Effect with Repeated Irradiations

Given experiments provide proof not only of the expressed protection at sublethal doses, which manifest themselves at the cellular level, but also of the insignificant changes, in this case, of the amount of FUD.

Very convincing evidence of the effectiveness of protectors at sublethal doses were obtained in experiments on the restoration radioresistance of mice with repeated irradiation [255]. By determining the $LD_{50/30}$ of control mice and animals, protected by AET or mexamine (respectively, 590 ± 22, 900 ± 20 and 880 ± 10 rads), three lots of intact mice (about 320-360 animals to each lot) were subjected to irradiation in doses consisting of half of that found in $LD_{50/30}$: the first of them (control) at a dose of 295 rads, and the second and third (experimental) at a dose of 450 rads. The experimental animals were procured before the irradiation by AET or mexamine. Later on 2, 6, 13 and 20 twenty-four hour periods

following the first irradiation of the mice, they are subjected to repeated exposure, in order to determine the $LD_{50/30}$.

The residual damage from the first irradiation at the moment of repeated exposure was exhibited in the form of differences between the $LD_{50/30}$ at single and repeated irradiation. As can be seen from Fig. 19, the dynamics of restoration of the resistance of protected animals, in principle, is not different from the control and is even characterized by a high rate.

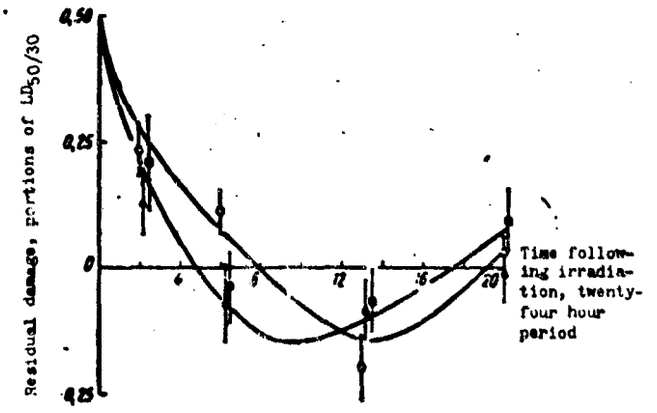

Fig. 19. Dynamics of the restoration of resistance in mice following irradiation under conditions of using protectors: O – control; ▲ – AET; ● – mexamine.

Consequently, the protectors, introduced prior to the first irradiation at a dose of 450 rads, are brought down to a dose of approximately 300 rads, i.e., FUD consisted of 1.5, just as in the determination of $LD_{50/30}$ under conditions of lethal irradiation [307].

One need not be reminded of the fact that the restoration radioresistance proceeds during the period of expressed aplasia of the bone marrow. Consequently, the determined state of radioresistance of an organism in such a way, does not coincide with the conventional estimate of injury based on clinical criteria, reflecting, obviously,

the characteristics of the preserved cellular population of the bone marrow, the research of which should be the object of a special investigation.

The maximum of cellular regeneration (10-16th twenty-four hour period following irradiation, see Fig. 10) during hyperplasia of the bone marrow corresponds to the period of increased radioresistance, which in itself, probably, is the reason for the increase in the resistance of the organism to irradiation.

Results of the described experiments confirm the established point of view about the fact that the protective effect of protectors over the range of moderately lethal doses consists of the decrease in the initial damage to the bone marrow, which shows up at these doses of a limiting system, with a constant FUD based on the criterion.

The obtained results served as a basis to check the validity of the conclusion about the relative independence of the protective effect from the radiation dose, and within the known limits as well as from the preliminary radiation exposure in the experiments with the introduction of the protector during the process of irradiation [372, 373].

Such investigations are also interesting from the viewpoint of using the protective means after the beginning of irradiation, specifically under special and emergency situations.

Experiments are run in the following manner. After irradiation at doses of 150, 300 or 450 rads the exposures are interrupted, 7 mg of cystaphos is injected intraperitoneally to the mice and after 15 min irradiation is continued, respectively at doses of 675, 450 and 225 rads. The values of the last doses were selected in such a way that by taking into account FUD, equal to 1.5, the cumulative dose would amount approximately to 600 rads, i.e., $LD_{50/30}$.

As can be seen from Fig. 30, the calculated protective effect of a protector and that observed in experiments differ slightly,

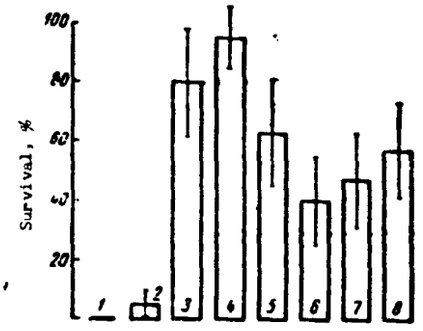

Fig. 20. Effectiveness of cystaphos, introduced during the process of irradiation (reliable limits at $R < 0.05$): 1 – 750 rads; 2 – 300 rads + 400 rads; 3 – cystaphos + 750 rads; 4 – cystaphos + 300 rads + 450 rads; 5 – cystaphos + 900 rads; 6 – 150 rads + cystaphos + 675 rads; 7 – 300 rads + cystaphos + 450 rads; 8 – 450 rads + cystaphos + 225 rads.

although cystaphos was used over the range at doses of 225-675 rads against the background of preliminary irradiation at doses of 450-150 rads. In all cases, at the 30th twenty-four hour period about one half of the animals survived which coincides with the amount of FUD, found in the experiments during irradiation at lethal doses [307], and does not correspond to the data on the weakening of the protection at an exposure of relatively small doses or with preliminary irradiation and with additional information on loading of injury during irradiation at sublethal doses. Graphic demonstrations to the contrary are presented in Fig. 21, from which it is evident that the theoretically forecasted quantity of FUD, accepted for all doses is equal to 1.5, was confirmed in the experiments, due to the fact that sum total effect of irradiation was close to that expected (allowing for the protection). If, at light and sublethal doses the protection were lacking, injury would be more than redoubled, and then one should expect 100% mortality of animals since cumulative dose in all cases would attain the absolute lethal or supralethal value (825, 750 or 675 rads).

The obtained results will agree completely with the Langendorf' data [374] about 100% survival of mice under the effect of AET at a moderately lethal dose (590 rads) and about a constant FUD for serot n over the range of doses, which have caused 25, 50 and 75% mortality of control animals [375]; also from observation by I. B. Bychkovskaya and G. S. Novoselov [362] about the constant value of FUD for AET over the range of doses of 300-1200 rads, the results

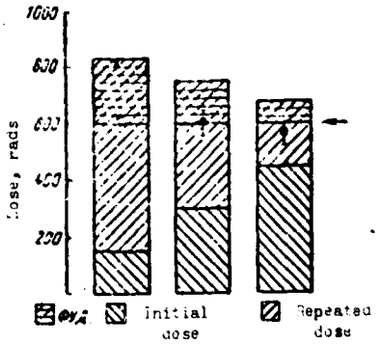

Fig. 21. Expected degree of injury when summing up the doses taking into account the amount of FUD, equal to 1.5 (shown by a pointer), and the actually obtained injury in experiments (experimental points and reliable limits when $P < 0.05$).

agree. Approximate data were also received for MEA on cystamine [376], as well as heterocyclic imidazole compounds [377].

From the early investigations of Patt and coworkers [363] the correlation between the protective effect of protectors on survival and their effect on radiation injury of a hemopoietic system over a wide range of doses is known which showed the stable weakening by cysteine (approximately 40%), of atrophy of the spleen, and the lowerings of number of granulocytes and lymphocytes at doses of 50-1000 rads.

A similar quantity of FUD (about 1.5) for MEA is obtained as criterion of survival also during the calculation of the number of macrocolonies in the spleen or granulocytes and lymphocytes of mice, irradiated at doses of 600-1500 rads [376].

The protection by MEA (FUD is equal to 2.5), AET and by serotonin (FUD is equal to 1.5) of the erythropoiesis of mice based on the inclusion of radioactive iron in erythrocytes with irradiation at a dose of 75 rads is shown [379-382]. At the same radiation dose the rats were not protected with either the serotonin, or the MEA based on this criterion [379], and homocysteinethiolactone, effective at the lethal dose, does not turn out to be effective on the erythropoiesis of mice at a dose of 75 R [381].

Thus, the lowering of the protection with fractionated irradiation cannot be explained as being ineffective for protectors

during the action of single sublethal doses, and likewise cannot be explained by the effect of preliminary irradiation.

The Dependence of the Protective Effect on the Intervals Between Irradiations and Amount of Single Doses

Protection of the bone marrow manifests itself at all investigated doses to an equal degree and hardly depends on previous radiation exposure; therefore, it should show up completely also with fractionated irradiation, being governed only by the degree of restoration of hemopoiesis at the time of the next irradiation.

Experiments whose results are stated below, confirmed the validity of such an assumption.

Based on the data about the periods of restoration of the number of karyocytes in the bone marrow for screening animals (25-30th twenty-four hour period at a lethal dose, and 10-14th twenty-four hour period at a sublethal dose, see Fig. 10), repeated irradiations of animals are produced with corresponding intervals, being applied prior to their respective protectors. With double or triple irradiation at a dose of 700 rads with an interval of 30 twenty-four hour periods, the protective features of the protectors were sufficiently exhibited (Table 14). During the irradiation at a dose of 700 rads, produced over 14 twenty-four hour periods following the initial exposure at a dose of 400 rads, the protective effect of AET was highest, which can explain that observed during this time period of increased radioresistance (in the control 50% of the mice survived) in accordance from the results of the described experiments (see Fig. 19).

At the same time, as can be seen from Fig. 22, in the displayed effectiveness of the chemical protection at each irradiation, the latter has a tendency to be lowered. Decrease in the effectiveness of protection from 91 to 72% (curve 1) permits one to conclude that at such intervals between irradiations there is a substantial restoration of the basic radiosensitive systems of the organism.

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Table 14. Effectiveness of the protection of mice with fractionated irradiation at wide intervals (number of survived animals at the 30th twenty-four hour period following the last irradiation), %.

Preparation, mg/kg	700 rads 2 times over 30 twenty-four hour periods	700 rads 3 times over 30 twenty-four hour periods	400 rads + 700 rads over 14 twenty-four hour periods
-	0	0	50 ± 11
ABT, 150	77 ± 8	79 ± 6	95 ± 4
Cystaphos, 350	60 ± 9	–	–
Mexamine, 75	85 ± 6	57 ± 9	90 ± 6

Note. The protector was introduced intraperitoneally for 5-10 min prior to each irradiation.

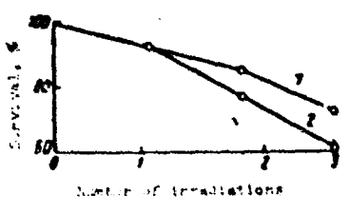

Fig. 22. The effectiveness of protection with repeated irradiations at a dose of 700 rads with an interval of 30 twenty-four hour periods: 1 – number of survived mice at the given irradiation; 2 – number of survived mice of the total number, introduced in the experiment.

One should specify that by mentioning the "restoration" or "complete protection," here and further on we have in mind only the immediate effects of irradiations, evaluated for the survival or restoration of the number of hemopoietic cells over 30 twenty-four hour periods following irradiation. In this case normalization in a number of vital systems still does not go on which at the usual vivarium capacity of animals, also creates uncontrolled conditions of the experiment.[1]

[1] In a preliminary communication about results of the first experiments, carried out on a small number of animals (a total of 54), protective effect of ABT and mexamine remained at a level of 90-100% for all three irradiations [5].

In subsequent experiments (Table 15) the radiation doses varied as well as the intervals between them. At shortened intervals up to 5 twenty-four hour periods, and with a reduction in a single dose to 400 rads the protective effect was sharply reduced.

Table 15. Protective effect of protectors under different conditions of fractionated irradiation.

Series of experiments	Conditions of fractionating	Protector	Number of animals, surviving at the 30th twenty-four hour period following the last irradiation	Average duration of life, twenty-four hour period
1	400 rads for 4 times over 5 twenty-four hour periods	–	3±1.4	18.9
		AET	18.6±3.4	31.5
		Cystaphos	3.3±3.3	29.8
		Mexamine	10.0±5.5	26.7
	300 rads for 4 times over 5 twenty-four hour periods		30.7±7.4	—
2	300 rads for 4 times over 2 twenty-four hour periods	–	11.9±2.8	9.7
		AET	66.4±7.6	13.7
		Cystaphos	61.1±11.4	12.7
3	400 rads for 3 times over 3 twenty-four hour periods	–	0	12.6
		AET	80.0±7.4	14.5
		Cystaphos	80.0±7.4	13.7
4	400 rads for 2 times over 1 twenty-four hour period	–	20.0±6.4	10.9
		AET	82.0±6.1	10.6
		Cystaphos	90.0±6.9	—
		Mexamine	70.0±10.5	9.8

Note. Doses and means of using the protectors are the same as in Table 14.

Figure 23 represents the dynamics of karyocytes in bone marrow of animals in this series of experiments, of protected AET which exhibit the condition of the pool at the moment of the following irradiation, at intervals between them as well as over 20 twenty-four hour periods following the last exposure. The number of cellular elements for protected animals during the whole span exceeds the corresponding control indexes, since the difference between the experiment and the control each time amounts to approximately $2 \cdot 10^6$ cells, just as in the experiments with a single exposure (see Fig. 10).

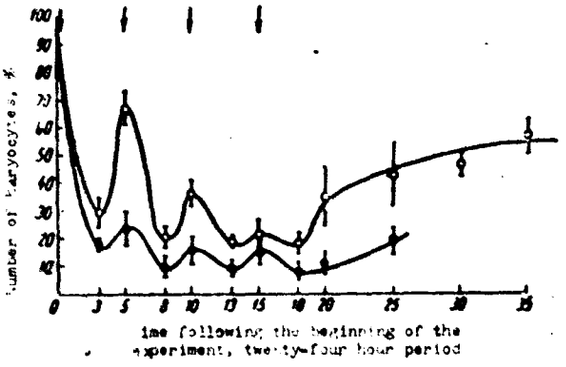

Fig. 23. Change in the number of cells in the bone marrow of mice with fractionated irradiation (4 times for 400 rads over 5 twenty-four hour periods) under the effect of AET. Pointers – days of irradiation. The data of joint experiments by V. G. Ovakimov and O. P. Ol'shevskaya [383]: ○ – experiment; ● – control.

As can be seen from Fig. 23, at the moment each subsequent irradiation of approximately half of the cells is restored, since rate of rising curve with each one immediately diminishes (expecially after the 3rd and 4th irradiations), reflecting deceleration of the rate of reparation. In connection with this toward the end of the observation – over 20 twenty-four hour periods following the last irradiation (35th twenty-four hour period of the experiment) – only half of the pool of the bone marrow is restored, while with a single exposure at this period normalization of the karyocytes takes place (see Fig. 10).

The deceleration of restoration distinctly manifests itself during the analysis of the peripheral blood (Table 16), from which it is evident that toward the end of the observation, the number of leucocytes comprises only 1/3 of the original.

Thus, despite the certain protection of the determined fractions of the cells of the bone marrow with each irradiation, toward the end of the experiment, the incompleteness of restoration of karyocytes,

Table 16. Change in the average number of leucocytes (in thousands per 1 mm^3 of blood) in mice with fractionated irradiation (4 times at 400 rads at intervals of 5 twenty-four hour periods) under the effect of AET.

Time of the investigation	Control	Experiment
3 twenty-four hour periods following the 2nd irradiation.....	0.4 0.2-0.7	1.6 1.4-2.0
3 twenty-four hour periods following the 3rd irradiation.....	0.4 0.2-0.6	0.8 0.6-0.9
3 twenty-four hour periods following the 4th irradiation.....	0.4 0.3-0.4	1.0 0.7-1.3
5 twenty-four hour periods following the 4th irradiation.....	0.5 0.3-0.9	2.1 0.7-3.6
10 twenty-four hour periods following the 4th irradiation.....	0.9 0.4-2.1	1.2 0.5-2.0
15 twenty-four hour periods following the 4th irradiation.....	-	2.2 1.1-5.9
20 twenty-four hour periods following the 4th irradiation.....	-	2.9 2.0-3.8

producing the deficit of cells in the bone marrow and blood is revealed which, probably, also is involved in the lowering of the survival of the experimental animals.

Amid these facts alone the decrease in the single radiation dose from 400 to 300 rads, i.e., to an amount, even less than FUD, protectors are used, the survival of the control animals to 40% (the second experiment of the 1st series, see in Table 15) increases.

Thus, despite the retention of the amount of FUD of the protectors relative to the number of cells in the bone marrow with each irradiation, the protection of the organism based on the criterion of survival seems weakened.

An attempt to facilitate the outcome of radiation injury by using antibiotics did not result in success (Table 17).

Table 17. Survival of mice with quadruple irradiation of a single dose at 400 rads over 5 twenty-four hour periods with the combined utilization of AET and streptomycin.

Preparation and dose, mg/mouse	Number of mice	Survived at the 30th twenty-four hour period following the last irradiation		Average duration of life, twenty-four hour period
		Number	%	
—	30	1	3.3	14.1
AET, 7	29	5	17.2	32.5
streptomycin, 3	30	0	0	25.9
AET, 7 + streptomycin, 3	69	8	11.6	32.1

Note. Streptomycin is introduced subcutaneously over two weeks, beginning with the second irradiation.

Obviously, the protective effect can be increased:

1) by using protectors, which are characterized by a large coefficient of FUD, taking into account the expressed weakening of the initial damage and preservation of a correspondingly larger cellular fund;[1]

2) by reducing the deficit of hemopoiesis.

As can be seen from the results of experiments in the 2nd and 3rd series (see Table 15), with a reduction of the overall time of irradiation from 15 to 6 twenty-four hour periods (300 rads for 4 times over 2 twenty-four hour periods of 400 rads for 3 times over 3 twenty-four hour periods) protective effect increases, by approaching that observed in a single exposure.

The dynamics of cells in the bone marrow in intervals between irradiations, studied in one of these experiments by Ye. I. Lavrenchik (Fig. 24), is suggestive of the corresponding data, obtained with a

[1]The results of corresponding experiments can be found in Chapter V.

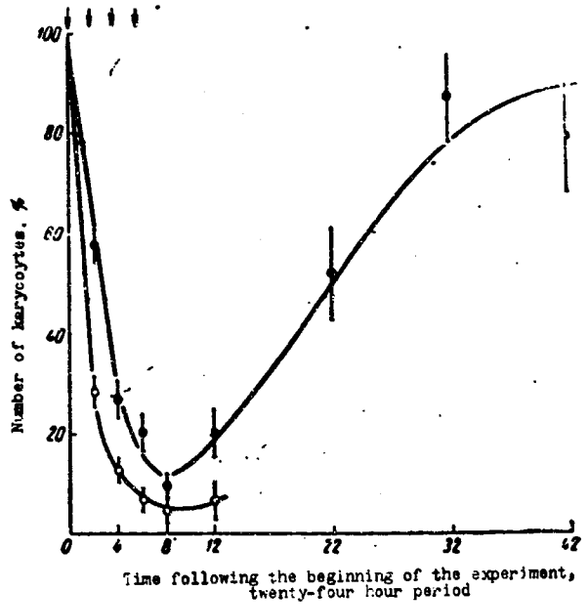

Fig. 24. Change in the number of cells in the bone marrow of mice with fractionated irradiation (4 times at 300 rads over 2 days) under the effect of AET. Pointers — days of irradiation: ● — experiment; ○ — control.

fourfold irradiation at a dose of 400 rads at intervals of 5 twenty-four hour periods, (see Fig. 23); however, it differs from them by the considerable shortening of the period of aplasia of the bone marrow, by the accelerated rate of restoration and by the time of the onset of normalization which, obviously, also governs the increase in survival.

With double irradiation at a dose of 400 rads with a twenty-four hour period interval, the protective effect is not substantially different from the protective effect with a single lethal irradiation (4th series, see Table 15).

Thus, at all the investigated doses under conditions of fractionated irradiation the protectors each time shield a determined portion of the hemopoietic cells and, by weakening the same initial injury, facilitate the subsequent reparation. The degree of protective

effect depends on the intervals between irradiations, on single doses and total doses. All these factors, regulating the kinetics of the restorative processes, quantitatively determine the integral manifestation of protection based on the survival of the animals.

Analysis of the Reasons for Weakening the Protection with Fractionated Irradiation

Three possible reasons for weakening protection with fractionated irradiation were investigated:

1) effect of irradiation on the distribution of protectors in the organism;

2) decrease in the protection with the lowering of a single dose of irradiation;

3) effect of preliminary irradiation.

In experiments with S^{35}-AET it was shown that irradiation in itself facilitates a certain retarding of the protector in individual organs, which can be partially associated with the increase in sensitivity of irradiated animals to thiol preparations. However, these cannot explain the substantial reducing of the protective effect, since it is known that upon introduction prior to single exposure of set toxic amounts of protector leading to the death of a considerable proportion of the animals, mice surviving the first two twenty-four hour periods, are distinguished subsequently by high survival. The assumption of the existence of a positive correlation between the individual radioresistance of animals and their resistance to the toxic action of the protector [177] is entirely logical. In this instance the amount of protector, being optimum for the radioresistant individuals, can be toxic for the most radiosensitive ones. Such an explanation, however, is limited by concrete conditions of the experiment. Actually a newly introduced species of animals of linear and individual sensitivity to protectors [384] in combination

with its intensification under the effect of irradiation cannot always be taken into account in the experiment when selecting the optimum quantities of protector.

By us izucena the radioresistance of noninbred (white), inbred (BALB, $C_{57}Bl$, DBA and CBA) mice, and hybrids (CBA × $C_{57}Bl)F_1$ and (DBA × $C_{57}Bl)F_1$ in comparison with their sensitivity to AET and mexamine [385].

From Table 18 it is evident that both according to radiosensitivity, and sensitivity to protectors, the animals can be differentiated within the limits of 8-35%. If we were to take white noninbred mice as a basis, then among the investigated parameters in most cases a positive correlation [BALB, C_{57}, Bl, DBA, (DBA × × $C_{57}Bl)F_1$, (CBA × $C_{57}Bl)F_1$] is really observed; however, inverse interrelations (CBA) or selective sensitivity, for example, the resistance of the hybrids (CBA × $C_{57}Bl)F_1$ to mexamine, correlating with the radioresistance, with undifferentiating sensitivity to AET (Fig. 25) takes place.

If we were also to assume that at doses, less than LD_{50}, mainly the defective animals will perish, which are primarily affected by the indirect effect of protectors [386], then the combination of shown factors can overlap the protective effect of the protectors in relationship to the bone marrow, since role of the latter in the outcome of injury at such levels of radiation injury is relatively small.

The shown complications can be eliminated by the careful selection of the optimum protective amount of protector under actual experimental conditions taking into account the condition of the preparation, the sexes, species, age, to strain of animals, etc. In accordance from the results of the experiments, in which the weakening of protective effect with a simultaneous decrease in the amount of introduced protector and radiation dose [6] is shown, such an optimum number of preparation should "work" well at any level of radiation exposure.

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Table 18. LD_{50} AET and mexamine (mg/kg) and $LD_{50/30}$ (rads) for mice of different lines.

White			BALB		
Irradiation	AET	Mexamine	Irradiation	AET	Mexamine
555±10	194±8,3	230±1,2	460±9,5	178±3,3	190±7,5

Continuation

$C_{57}Bl$			DBA	
Irradiation	AET	Mexamine	Irradiation	AET
510±7,3	178±2,6	202±7,5	620±22	220±1,1

Continuation

DBA×$C_{57}Bl$		CBA		
Irradiation	AET	Irradiation	AET	Mexamine
635±17	239±7,3	665±1,1	192±9,5	210±5,9

Continuation

CBA×C_{57} Bl		
Irradiation	AET	Mexamine
695±1,2	194±7,1	263±7

Note. $LD_{50/30}$ was determined based on the survival of mice following their overall X-ray irradiation at doses of 400, 475, 550, 625, 700 and 775 rads; LD_{50} - on intraperitoneal introduction of the protectors from the calculation of 100, 125, 150, 175, 200, 225, 250 and 275 mg/kg.

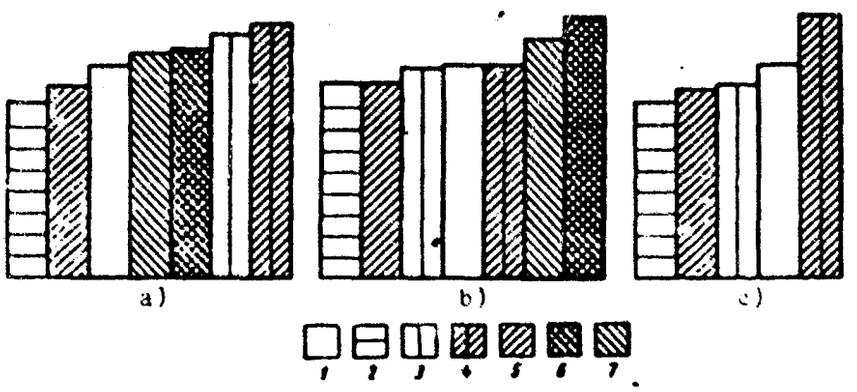

Fig. 25. Relative radioresistance (a) and stability to the toxic effect of AET (b) and to mexamine (c) mice; the corresponding parameters for white mice are taken as 1.0: 1 - white noninbred mice; 2 - BALB mice; 3 - CBA; 4 - CBA × $C_{57}Bl$; 5 - $C_{57}Bl$; 6 - DBA × $C_{57}Bl$; 7 - DBA.

As can be seen from Tables 19 and 20, this actually occurs.

Table 19. Dependence of the protective effect on the amount of introduced protector with double irradiation of mice at a single dose of 400 rads with an interval of 24 h.

Preparation	Amount of the preparation, mg/kg	Number of mice	Number of animals, fallen from the toxicity of the preparation	Survived at the 30th twenty-four hour period	
				Number	% (from that calculated having fallen due to toxicity)
Physiological solution	0,2 ml	50	—	11	22
AET	150	50	10	34	85
	75	50	—	46	92
	38	50	—	36	72
Cystaphos	350	30	—	29	97
	175	40	—	20	50
	88	40	—	7	17,5

Table 20. Dependence of the protective effect on the amount of introduced protector at quadrupled irradiation of mice at a single dose of 300 rads at intervals of 48 h.

Preparation	Amount of the preparation, mg/kg	Number of mice	Number of animals, fallen from the toxicity of the preparation	Survived at the 30th twenty-four hour period	
				Number	% (from that calculated having fallen due to toxicity)
Physiological solution	0,2 ml	30	—	1	3
AET	150	30	9	17	80
	75	30	—	21	70
	38	30	—	12	40
Cystaphos	350	30	—	18	60
	175	30	—	9	30
	88	30	—	2	7

The experiments, the results of which have been presented in Tables 19 and 20, were made in the form of two series of experiments at a different time with an interval of four months. In one of them death was not observed due to the toxicity of the preparation, but in the other, in both schemes of the fractionating of AET in the

occurs.

amount of 150 mg/kg death occurred in about 1/3 of the animals in the first hours following injection.

Prior and after these experiments upon introducing the shown amounts of AET only individual animals perished; therefore, there is a basis to assume that in this case increased sensitivity of the mice to the preparation was observed.

Two conclusions, stemming from the results of the considered experiments, are highly important.

1. In both schemes of fractionating, the results of the early experiments [6] about weakening the protective effect with a simultaneous decrease in the amount of protector and of a single dose of irradiation, were clearly confirmed. For significant protection, consequently, it is necessary to introduce equal sufficiently bulky (optimum) amounts of preparation at any radiation doses.

2. In experiments, in which the mice perished from the toxic effect of AET, absence of the effect of toxicity on the degree of protective effect is demonstrated since among the animals to which the introduced dose of preparation (aside from quite evident manifestations of toksicosis) is transferred, during the 30th twenty-four hour period of observation a sufficient number survived.

Consequently, the optimum amount of protector "works" equally well at any level of radiation exposure.

Results of these experiments impress the idea of verifying the protective effect of the lowered quantities of protectors during the irradiation at lethal doses. It turned out that the lowering to a 1/3 dose of AET from the conventional, and cystaphos taken from the freely transferable form [387] is not accompanied by the weakening of the protective effect (Table 21).

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Table 21. Dependence of the protective effect on the amount of introduced protector during the irradiation of mice at a dose of 700 rads.

Preparation	Amount of introduced preparation, mg/kg	Number of mice	Survived at the 30th twenty-four hour period	
			Number	%
Physiological solution	0,2 м l	40	0	0
AET	150	40	30	95
	100	40	39	98
	75	40	32	80
	38	40	25	60
	500	40	38	95
Cystaphos	350	40	37	92
	250	20	17	85
	125	20	14	70

Thus, as optimum doses of protector, both at single and fractionated irradiation under our conditions one should calculate for 100 mg/kg AET and 250-300 mg/kg of cystaphos. They provide a high protective effect without toxic manifestations.

Confirmation of these considerations was also obtained for maximum. In an experiment on mice-hybrids $(C_{57}Bl \times CBA)F_1$, subjected to irradiation with protons at doses of 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400, 1500 and 1600 rads, mexamine in the amount of 50 mg/kg exhibited a protective effect throughout the range of doses, causing injury to the bone marrow, without any hint of weakening the protection or manifestation of toxicity with the lowering of tne dose of irradiation. The coefficient of protection based on the survival over 30 and 60 twenty-four hour periods following irradiation amounted to 1.0 at minimum doses, causing death in the control, and then monotonically was reduced with an increase in the doses of irradiation.

Unfortunately, we arrived at such a conclusion only very recently, in connection with all the experiments, the results of which have been already presented or will be described in subsequent chapters, and which conventional doses of both protectors were used.

Thus, the experimental material, given in the data and in Chapter IV, quite persuasively testifies to the fact that over a considerable range of nonlethal, moderately lethal and lethal doses (150-700 rads), the protective effect of protectors has been clearly expressed. In this case, both in relationship to the bone marrow as well as to survival in experiments with single, repeated irradiation or with the utilization of protectors in process of irradiation it was shown that FUD in the investigated range of doses for the given protector changes insignificantly, and within known limits depends on the preceding irradiation. In fact the amount of FUD and the degree of reduction associated about it of initial injury to the bone marrow basically determine the success of the chemical protection with fractionated irradiation.

The second determining factor in this sense is the amount of a single radiation dose, and third – the intervals between the individual irradiations. In their totality, these three factors regulate the complex kinetics of reparative processes of the bone marrow, the intensity and full value of which cannot be described by a simple monofunctional mathematical model, as was done in [388].

In examining the kinetics of restoration of a prolifirational pool of a bone marrow in mice, protected by AET under different conditions of radiation exposures (Fig. 26), it is possible to see that with an increase in the radiation dose or during the transition from a single exposure to the fractionated rate of reparation it is noticeably reduced.

After a single exposure at sublethal doses (270 and 400 rads) the highest rate of restoration with an average rate of $3 \cdot 10^6$ cells per twenty-four hour period is noted. At an absolutely lethal dose during the first three twenty-four hour periods the rate of reparation is the same, and then is reduced by more than two times (up to $1.5 \cdot 10^6$ cells per twenty-four hour period), in connection with the fact that the original level is attained considerably later.

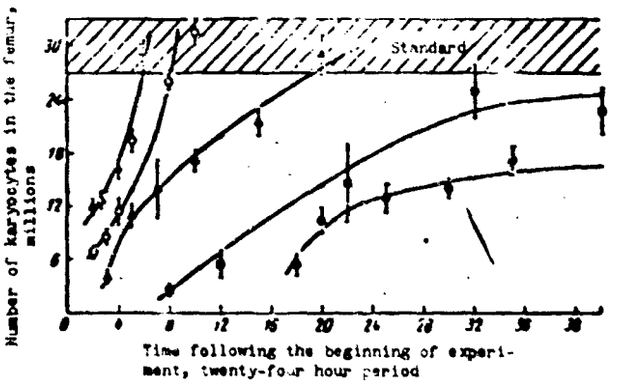

Fig. 26. Kinetics of restoration of karyocytes in bone marrow of mice under different conditions of radiation exposure. With single exposure at doses: 270 rads (▲), 400 rads (○) and 700 rads (●); with fractionated irradiation of 300 rads × 4 over 2 twenty-four hour periods (■) and 400 rads × 4 over 5 twenty-four hour periods (●).

As a result of the fractionated irradiation, the rate of restoration is still lowered more. With the overall duration of irradiations of 6 days (300 rads for 4 times over 2 twenty-four hour periods) $0.7 \cdot 10^6$ cells per twenty-four hour period is restored. Over a two-week hold period of the bone marrow in the state of aplasia (400 rads for 4 times over 5 twenty-four hour periods) following a short-time (during 2 twenty-four hour periods) period of active restoration ($2.4 \cdot 10^6$ cells per twenty-four hour period) its rate falls to a minimum value ($0.37 \cdot 10^6$ cells per twenty-four hour period). As shown, under this condition of irradiation the minimum effect of protection (see Table 15) is observed.

Consequently, the rate of reparation of the bone marrow is affected unfavorably: the increase in the radiation dose and duration of fractionating. The latter has a relative value, since it negatively has an effect only at those such intervals between irradiations when restoration of original level is not attained, as a result of which the bone marrow is in a prolonged state of aplasia.

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Apparently, in associations with the lowering of the protective effect of an eight-fold irradiation at a dose of 200 R with twenty-four hour intervals, the overall prolongation amounts to about two weeks [6].

With repeated irradiations in lethal doses from the 14th and 30th twenty-four hour intervals, the protective effect is clearly shown although its absolute value diminishes with each fraction.

Other researchers also arrived at an analogous conclusion in the research on the protective effect of serotonin on mice, subjected to triple overall irradiation at a lethal dose from the 30 twenty-four hour intervals [389, 390]. Data in the research [391-393] are also evidence of the decrease in the reparational rate, induced by the change in the functional state of the bone marrow as a result of previous irradiations.

Not withstanding the fact of the lowering of the functional activity of the hemopoietic system taking place with an increase in the cumulative dose or at widely spaced periods after irradiation, there exists the result of the breakdown of neuroendocrine regulation [394, 395] as manifestations of the irreversible component of radiation injury determining the lowering of the series of adapti possibilities of an organism [395-398]. During the irradiation of the upper half of the trunk of rats and dogs, specifically the head, the rate of reparation of the pathological shifts seemed to be lower, but the residual component of radiation injury somewhat higher, than with an equivalent irradiation of the remaining part of the body. This was confirmed by clinical and physiological data, which authors in [398] interpreted as trace disturbances in the activity of the central nervous system even as late as 18 months following the pre liminary exposure.

Difference in the rate of reparation depending on local or overall irradiation, and also on the amount of dosage is shown as an example of such active proliferated organs, as the spleen, mucous intestines and testicles [399].

If we are faced with the fact that the protectors have less effect on the irreversible component of injury (as can be seen from a further account, this assumption is not grounded), then with an increase in the cummulative dose of irradiation some unprotected part of the injury can accumulate in the organism [25]. Consequently, with fractionated irradiation, despite the preservation of the number of FUD of this or another protector, subsequent reparation will proceed in worse fashion everywhere equally than following a single irradiation. Such an explanation is a more acceptable assumption about the preferential protection by the protectors of the restorative processes or which control subsequent "subsystems" [177, 238] as a reason for weakening of the protection with the lowering of the radiation dose with assumption that at slightly lethal radiation doses, the processes of restoration still do not suffer. The results, obtained on research of the restoration of radioresistance of an organism to repeated irradiation, do not confirm such a possibility; the rate of restoration of the control mice is even somewhat lower than for protected, irradiated respectively, at doses of 300 and 450 rads (see Fig. 19). Consequently, the "protection of restoration" was also observed during irradiation at a slightly lethal dose of 450 rads.

Two works were completed recently, clearly demonstrating the protective effect with fractionated irradiation. In one of them the weakening of radiation epilation by serotonin with repeated local irradiation of guinea pigs [400] was shown. In the other, of the already mentioned works [388], the results of using MEA with the most diverse variants of fractionating were analyzed. Authors came to the conclusion that only two factors determine the success of protection with fractionating: the number of FUD and the rate of restoration, which is constant for the given animal, aside from that depending on the intervals between the irradiations and the previous irradiation. Then if the dose, obtained by animals, exceeds the so-called effective dose (cumulative dose with the correction for restoration and number of FUD), then, accordingly to a simple mathematical model, death approaches towards the end of the 30th twenty-four hour period of

observation; [388]. The drawn conclusions will agree themselves with our conclusion; however, they do not completely consider the possible breakdowns of the adaptive mechanisms as a result of the increase in the cummulative dose. Among them a special mathematical analysis of the resotration of the hematopoietic systems following repeated irradiations showed that the complete adaptation does not take place [401]. The given data of quantitative analysis of the bone marrow itself do not leave any doubt of the value of the breakdown of the adaptive potentials of the organism.

It is impossible to rectify the data from all recently published works [375]. The authors of the voluminous material (3900 mice) have persuasively showed the constant FUD of serotonin with single exposure at doses, causing 25, 50 and 75% mortality of animals (1.51; 1.47 and 1.52, respectively). With repeated daily irradiation at a dose of 100 R, serotonin was less effective: for an $LD_{50/30}$ and $LD_{75/30}$ the FUD was equal respectively to 1.12 and 1.35. However, during the comparison of doses of single or fractionated irradiation, causing similar death in mice under conditions using serotonin, it turned out that the effect of fractionating and protective action of serotonin cannot be completely summarized. By analyzing these data, the authors considered it as an illegal presentation of the processes of restoration on the stimulation by protectors and gave preference to the fact of the decrease in the initial radiation injury.

The analysis of the time of extinction of the mice with fractionated irradiation is of specific interest. It was disclosed that the difference in survival of the control and protected mice manifests itself only after 18-20 twenty-four hour periods [375]; with an increase in the duration of the fractionated irradiation the second reason for the mortality is clearly uncovered which, apparently, also leads to a decrease in the amount of FUD during the analysis of $LD_{50/30}$. On the basis of these data one can assume that during the irradiation at small doses even up to the manifestation of marrow syndrome, the reason for death is the injury of the others actually not hemopoietic, of not yet identified vital systems, distinguished by high radiosensitivity and therefore poorly protected. Such a

possibility was discussed independently at a different time by N. I. Shapiro [178], by us [25] and by V. I. Suslikov [402]. It is possible that such a vulnerable place would turn out to be immune systems [403].

In conclusion there are several critical remarks.

1. The utilization of prolifirational activity of the bone marrow as the leading criterion of protection to a certain extent simplifies the problem of the latter. The complex symptom complex of the radiation syndrome includes systemic injury of the whole organism, the role of which, as indicated, is still hardly studied. Distinctly realizing the known bounds of such an approach, we selected it as a rational one, making possible the exarticulating of most critical link, the state of which adds to the quantitative calculation.

2. For these same reasons the requirements of a universal law to the approach of a estimate of the state of the organism in protected animals from the position of the theory of restoration of radioresistance are not satisfied. Above the fundamental differences between the clinical manifestations of acute radiation sickness were shown which are characterized by a strict periodicity in the development and the characteristic dynamics of restoration by a monotonic decrease in the residual phenomena of radiation injury. Special works [404, 405] were devoted to the examination of this problem. In accordance with their data let us state the following considerations:

a) a nonconformity is possible between the intensity of the temporary processes with the first and repeated irradiations;

b) the development of dissimilitude of the conventional estimated tests with first and repeated irradiations is not ruled out;

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c) in principle, it is impossible to obtain equal biological effectiveness of doses of the first and second irradiation in any of their combinations;

d) there is still insufficient grounds to completely extend all disclosed regularities to doses not causing death.

In justice to the first three considerations one can at least be certain in the example of the only conducted analysis of the rate of reparation in bone marrow depending on the conditions of irradiation. The fourth – is trivial.

All this, however, does not lower the value of the used method, especially since the drawn conclusions are considered as expressed limitations.

Conclusion

With fractionated irradiation in proportion to the accretion of the dose and duration of exposure, reproductive ability of the bone marrow is destroyed, the degree of which depends on the intervals between the individual irradiations and the amount of single doses. The lowering of functional activity of hemopoiesis is also observed at widely spaced periods following irradiation, when the quantitative composition of the prolifirational pool is restored. The shown breakdown should be considered as one of the components of an irreversible and, apparently, poorly protected component of radiation injury, being easily exposed by means of repeated irradiation.

Under these conditions the manifestation of chemical protection is hampered, although the amount of FUD of the protectors with each irradiation based on the study of the criteria hardly changes.

In principle, the effectiveness of the protection can increase either by lengthering the intervals between irradiations, or by utilizing the protectors with a high value of FUD.

CHAPTER V

ANTIRADIATION PROTECTION WITH THE COMBINED USE OF PROTECTORS

Despite the multiplicity of investigations, devoted to the search of protective means, the effectiveness of individual protectors still cannot be recognized with a high degree of satisfaction. The most intensively studied compounds (β-mercaptoethylamine [MEA] (МЭА), aminoethylisothiuronium [AET] (АЭТ), serotonin, mexamine) according to the various researchers, including our own, shield 40-100% of the mice, irradiated at a minimum absolute lethal dose [MALD] (МАЛД). Such a range in variation of the amount of protective effect is determined by the characteristics of the conducted experiments, conditions of the preparations, by the specific and individual differences in animals, by the state of the vivarium, and likewise by the various uncontrolled conditions of the experiment.

Aside from depending on the absolute amount of protective effect at a MALD with the foregoing, the activity of all protectors rapidly falls or completely disappears.

In striving to raise the effectiveness of the protection, many researchers used a complex of various substances and obtained positive results. Straube and Patt, for the first time, in studying the protective effect upon the simultaneous introduction of half doses to cysteine and MEA in mice, detected their additive action since the degree of protection did not exceed its magnitude upon the introduction of the complete dose of one of the protectors under conditions of separate utilization [406]. For dogs this mixture was more toxic

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than the complete doses of the individual protectors; moreover, a synergistic effect was observed [407]. The intensification of the protective effect was also described during the simultaneous utilization of cysteine with AET [408], with cyanides [156, 409-411], with sodium nitrite [412, 413], with histamine, aminoacetonitrile, sodium nitrous acid, 2,5-dioxyphenylalanine, by pyriodoxine and adenosine triphosphate [ATF] (АТФ) [414-417], natural polnucleotides, mucopolysacharides and even some synthetic polymers [418]. The protective effect of MEA is intensified by phenatine also by phenamine [419], reserpine [326] and ATF [156], and the protective effect of mercaptopropylamine [MPA] (МПА) – by sodium nitrite [156, 415]. Furthermore, the combination of tryptamine [420] or adrenaline with acetylcholine [421-424] was studied. Novocaine was combined with ethylenediaminetetracedic acid [EDTA] (ЭДТА), para-aminobenzoic acid and its isomers [425], methylene blue with aminothiazole [426], aminazine with phenatine [427], thiamine with narcotics [428].

Even during the early investigations of Ye. F. Romantsev [156] and V. G. Yakovlev [414] the synergism of the protective effect of cysteine with tryptamine was shown.

Recently, much research was done in the successfully combining of AET with hypoxia [429] and with such compounds, as dimethylsulfoxide [90], hydroxylamine [21, 430, 431], chlorpromazine, α-chloralose [432] in experiments on mice or rats, *p*-aminopropiophenone [433] or cysteine [408, 433, 434] applied to apes and *p*-aminopropiophenone [392, 435, 436] or with a complex, consisting of cysteine, MEA and para-diphenyloxide [407, 437], on dogs. In the latter case the highest protective effect was observed: 100% survival during irradiation at a dose of 775 R under conditions when LD_{100} = 450 R.

Apparently, the combined application of protectors is effective when simultaneously compounds with a supposedly different mechanism of action are used; for example, those causing hypoxia (indolylalkylamines, methemoglobin formers), and thiol preparations (cysteine, MEA, AET), the effect of which is less associated with the level of oxygen concentration.

At the same time the possibility of a synergistic effect from one type of protector (AET and cysteine) emphasizes the value of its cellular organ distribution.

The most promising trend was the combined application of compounds, belonging to the above described basic groups of protectors: mercapto- and indolylalkylamines. In 1957 P. G. Zherebchenko and coworkers [438-441] began systematic investigations in this direction. As a result they made the assumption that on the basis of synergism of protectors there is a different mechanism of protective action.

Presented below are the results of the early joint investigations [439, 440], and then those developed independently. As already indicated, magnitude of the protective effect of protectors depends on the varied uncontrolled circumstances. Therefore, for the research on the combined protection in each case corresponding control experiments were set up with the individual application of the protectors.

Taking into account that work which encompasses investigations, carried out over 5-6 years, the absolute quantity of protection is sometimes distinguished in individual experiments. However, this does not affect the authenticity of the fundamental conclusions in connection with the presence of control experiments in each case.

The Combined Application of Protectors with a Single Exposure at Lethal and Supralethal Doses

As can be seen from Table 22, during the individual application of tryptamine and MEA in quantities of 100, 50 and 175, 100 mg/kg 23, 10 and 36, 29% of the mice irradiated at a dose of 700 rads survived respectively. During the combined application of these preparations the synergism of their effect was observed, since the amount of protection in this instance exceeded the expected by a simple sum total of the effects of the corresponding doses from each protector.

Table 22. Effect of MEA and tryptamine during an individual and a combined application on the survival of mice (intraperitoneal injection for 5-10 min prior to irradiation at a dose of 700 rads).

Protector	Amount of protector, mg/kg as a base	Number of mice	Survived at 30th twenty-four hour period		Average duration of life, twenty-four hour periods
			M±m	T	
Physiological solution (control)	—	60	1,6	—	11,7
Tryptamine, HCl	100	30	23,3±7,8	3,03	16,8
	75	30	16,6±5,3	2,6	12,4
	50	30	10,0±5,6	1,4	12,8
MEA, HBr	175	30	36,3±7,3	4,6	16,0
	150	30	26,6±8,2	3,02	15,4
	100	30	29,9±5,5	4,08	14,8
Tryptamine, HCl + MEA, HBr	100 + 175	35	—	6,6* / 5,1	16,2
Tryptamine, HCl + MEA, HBr	75 + 150	40	—	6,3* / 4,5	19,2
Tryptamine, HCl + MEA, HBr	50 + 100	40	52,5±8,0	4,3* / 2,3	18,7

*In the numerator – degree of reliability of the excess of the effect of the mixture in comparison with the effect of tryptamine, in the denominator – in comparison with the effect of MEA during individual application.

The combined application of preparations governs the protective effect even at a higher dose of X-ray irradiation (800 rads), when the individual introduction of the protectors is almost ineffective (Table 23).

The summing up of the protective effect cannot explain the simple increase in the number of introduced substance, since upon the introduction of some preparations in quantities, exceeding the optimum, the protective effect neither increases nor decreases (Table 24). Analogous results were received even relative to mercaptoethylguanidine [442] and serotonin [14].

Table 23. Effect of MEA, MPA, histamine and tryptamine during individual and combined application on the survival of mice (intraperitoneal injection for 5-10 min prior to irradiation at a dose of 800 R).

Protector	Amount of protector, mg/kg as a base	Number of mice	Survived at the 30th twenty-four hour period		Average duration of life, twenty-four hour periods
			M±m	T	
Physiological solution (control)	—	20	0	—	8,4
Histamine, 2HCl	350	20	20±9,2	2,1	10,0
MEA, HBr	175	20	10±6,5	1,5	14,5
MPA, HCl	150	20	0	—	10,1
Tryptamine, HCl	100	20	0	—	11,2
Tryptamine + MEA	260 112	20	55±12,5	2,4* 3,3	13,3
Tryptamine + MPA	100 150	20	45±12,5	3,7** 3,7	15,8

*In the numerator the degree of reliability in comparison with the effect of histamine, in the denominator – in comparison with effect of MEA during individual application.

**The same as in the comparison with the effects of tryptamine in MPA.

Table 24. Effect of the number of introduced protector on the degree of protective effect on mice (intraperitoneal injection for 5-10 min prior to irradiation at a dose of 700 R).

Protector	Amount of protector, μ/kg as a base	Number of mice	Survived at the 30th twenty-four hour period	
			Number	%
Physiological solution (control)	—	30	1	3,3
MEA, HCl	150	40	24	60,0
	225	20	10	50,0
Tryptamine, HCl	100	110	41	37,0
	150	49	11	22,4
	200	30	5	16,8
AET, 2 HBr	150	40	37	91,0
	200	35	28	80,0
	300	20	7(12)*	87,0

*In the brackets - the number of mice, fallen due to the toxic effect of the preparation in the 1st twenty-four hour period.

The combined application of known effective protectors is not always accompanied by synergistic action. As already mentioned, the combined application of MEA and cysteine revealed only the additive effect [406]. In Table 24a data are shown which are evidence of the additive effect of AET and cystamine (unsubstatiated differences).

Table 24a. Effect of individual and combined application of AET and cystamine on the survival of mice (internally for 1 h prior to irradiation at a dose of 700 R).

Protector	Amount of protector, μ/kg as a base	Number of mice	Survived at the 30th twenty-four hour period	
			Number	%
Physiological solution (control)	—	25	2	8
AET, 2HBr	400	35(7)*	18	64,3
Cystamine 2HCl	400	35	15	42,8
Cystamine + AET	300 300	30(2)*	14	50,0
Cystamine + AET	200 200	40	29	72,5

*In the brackets – number of mice, fallen due to toxic effect of the preparation during the 1st twenty-four hour period.

Thus, a clear summing up of the protective effect of the investigated preparations manifests itself only during the combined application of mercapto- and indolylalkylamines. This is shown most clearly in the example of the synergism of MEA and mexamine [441].

Apparently, the course of synergism of mercaptoalkylamines and indolylalkylamines – the different ways of realizing their antiradiation effect. The protective effect of indolylalkylamines, the typical representatives of which are serotonin and mexamine, associated with hypoxia, are caused by them in the radiosensitive organs [52, 70, 81, 84, 443, 444]. The majority of aminothiols, including AET does not cause the potential drop of oxygen in the tissues [84, 443, 445, 447] and does not possess a vasoconstrictory effect [52, 70, 81, 84, 443, 444]. During the simultaneous application of two groups of protectors their effect should be summarized. During the

simultaneous application of the shown groups of protectors, their effect should be summarized similarly, as was shown in the experiments according to the simultaneous application of MEA and local asphyxia of the bone marrow (see Chapter III) as well as other investigations [223, 267].

The successful application of complex thiols with compounds leading to tissue hypoxia, are proof of this – *p*-aminopropiophenone [392, 433, 435, 436], para-diphenyloxide [437], cyanides [412, 413], sodium nitrite [156, 410, 411].

At the same time it is possible to present in another way as well, the potentiation of the protective effect which comprises the differentiated protection of the individual radiosensitive organs. The corresponding experimental check showed the correctness of this assumption.

Based on the well known presentations about the so-called systemic death [180, 448-452] and corresponding means of estimating effectiveness of the protectors [448, 452], we studied the radioresistance of mice under the effect of protectors over the range of doses of 700-1200 rads. At these doses the protection of the bone marrow and intestines, the degree of injury of which is easy to take into account according to the periods of death of animals is of the fundamental value.

As is known, the simultaneous application of AET and serotonin is more effective than their individual introduction [417, 453]. It is known, likewise, that AET also shields the bone marrow [224, 286, 373, 453a, 454], as well as mexamine [222, 373, 441]. The intestines are well protected by AET [284-287]; in relation to mexamine direct information is lacking. However, it was established that approximate to the effect and structure, serotonin does not have an effect on the hyperemia of the vessels of small intestine [443] and hardly weakens the radiation suppression of mitoses in its crypts [454a]. It was expedient to compare the shown data according to the data on

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the effect of these protectors for the periods of death of animals at doses, causing preferential injury of the bone marrow or intestines, and in the case of the detection of the differentiated protection, to test their simultaneous application for an increase in the anti-radiation effect.

As the analysis of the average life of the control animals showed, a dose of 900 rads is the boundary between "marrow" and "intestine" death. With a subsequent increase in the doses, the mice perished from an intestinal syndrome at an average life of about 5 twenty-four hour periods (Table 25). The protective effect of AET appeared at all tested radiation doses: up to 1100 rads survival increased, and at 1200 rads the duration of life was substantially lengthened. For mexamine the upper threshold of the effect was detected – 900 rads, whereupon its effectiveness fell sharply, and at 1100 and 1200 rads, the time of death of the animals did not differ from time of death of the mice in the control. The protective activity of cystaphos up to 900 rads approximately coincides with AET and mexamine, but further on, gradually diminishes, manifesting itself, nevertheless, at all radiation doses (Fig. 27).

Results of the given experiments are in accordance with the mentioned information on the protection of AET of the bone marrow and intestines; analogous features, apparently, are exhibited by cystaphos, as well. Mexamine, being highly effective in relation to the bone marrow, hardly shields the intestines; this is confirmed by the assumption about the predominantly pharmacological nature of its protective effect [443].[1] In being consistent with the obtained data

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[1]At present it is shown that mexamine can weaken the injury of the intestines of mice and rats, if we irradiate the animal instantly at a high dose rate, and immediately (not later than 5 min) following the injection of the preparation (S. I. Yaroshenko and others. In the text, "Papers of the anniversary scientific session, dedicated to the [illegible] years of the Institute." Leningrad, Central Scientific Research Institute of Roentgenological and Radiological Investigation (TsNIRRI) [illegible], page [illegible]. [illegible], mexamine [illegible] a momentary spasm of the intestine vessels, and that is why [illegible]

Table 25. The effect of protectors on the survival and lifetime of mice at different doses of X-ray irradiation [307].

Radiation dose, rads	Number of mice	Number of survived animals, %	Average life, twenty-four hour periods	Cystaphos, 7 mg			AET, 3 mg			Mexamine, 1.5 mg			AET, 1 mg + mexamine, 1.5 mg		
				Number of mice	Survival, %	Average life, twenty-four hour periods	Number of mice	Survival, %	Average life, twenty-four hour periods	Number of mice	Survival, %	Average life, twenty-four hour periods	Number of mice	Survival, %	Average life, twenty-four hour periods
700	40	5	14.6	30	90	—	40	90	—	40	90	—	—	—	—
800	20	0	9.9	20	85	—	20	90	—	20	95	—	20	100	—
900	30	0	6.4	30	57	10.4	30	50	14.9	30	73	11.1	30(2)*	96	—
1000	20	0	5.3	20	30	8.7	20	60	14.6	20	10	8.1	30(1)	85	—
1100	20	0	4.7	20	15	7.5	20	25	7.1	20	0	5.2	30(2)	59	12.6
1200	20	0	4.6	20	0	7.1	20	0	8.2	20	0	4.0	20	20	6.7

*In the parentheses – number of mice, perishing during the first 24 h following exposure.

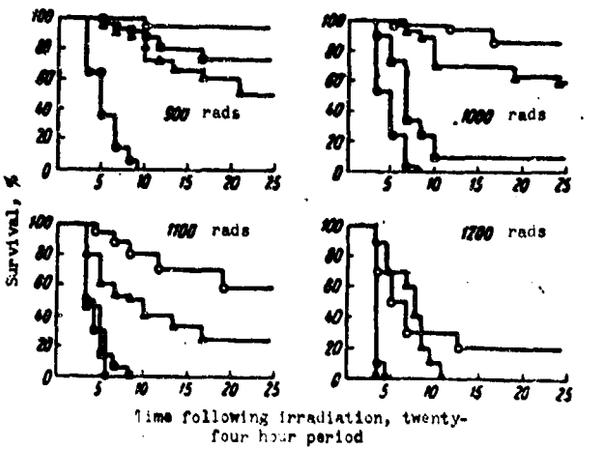

Fig. 27. Dynamics of death in mice at doses of 900-1200 rads under conditions of protection: ● – control; ■ – mexamine; ▲ – AET; ○ – AET + mexamine.

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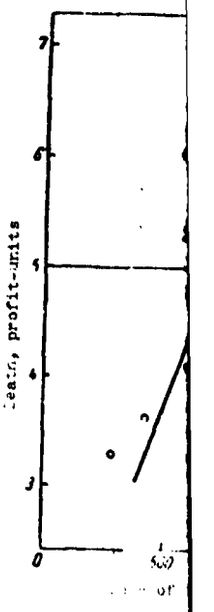

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it can be expected that during the combined application of AET and mexamine, an increase in the antiradiation effect can be achieved, if we strengthen the protection of the bone marrow.

In the preliminary experiments it was established that animals do not transport the simultaneous application of both protectors at the maximum protective doses, in connection with the fact that the amount of AET was reduced by three times.

As can be seen from Table 25, the complex of AET with mexamine increased the survival during irradiation at doses of 1000 and 1100 rads by 25-65% in comparison with the individual application of preparations. Lethal dose [$LD_{50/30}$] ($ЛД_{50/30}$) amounted to 1100 ± 26 rads for the complex, and for AET, mexamine and cystaphos, 950 ± 22, 925 ± 10 and 900 ± 25 rads, respectively, instead of 600 ± 12 rads in the control. The diminishing dose factor [FUD] (ФУД), calculated based on $LD_{50/30}$ is equal to 1.5; 1.54; 1.55 and 1.83, respectively, for cystaphos, mexamine, AET and the complex (Fig. 28).

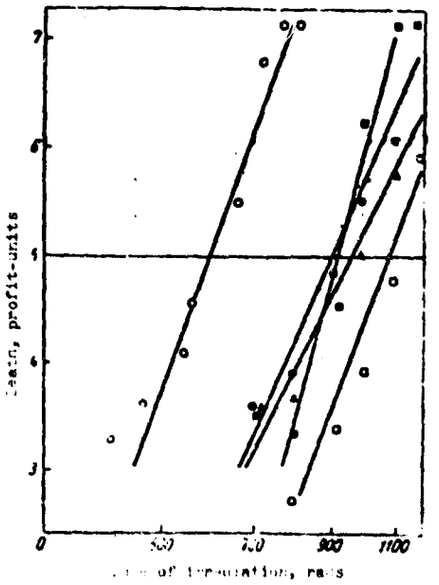

Fig. 28. Effect of protectors on the survival of mice, irradiated in doses of 700-1200 rads: ○ – control; ● – cystaphos; ▲ – AET; ■ – mexamine; ▣ – AET + mexamine.

Thus, in the synergism of the protective effect of the shown complex of protectors along with the proposed various mechanisms of the effect, the differentiated protection of the different systems has indubitable value. AET at an equal degree, shields the bone marrow and intestines, but mexamine – only the bone marrow. Owing to the many animals surviving the critical period of intestinal death (as a result of protection of AET), they also sustain the injury of the bone marrow, which under conditions of complex protection seems substantially less than during individual application of the protectors. Recently, other researchers also arrived at the analogous conclusion [455], having shown the considerable weakening of radiation injury in the cells in direct experiments of the intestinal crypt during the combined utilization of glutathone, AET and serotonin [456]. A considerable increase in the protective effect by the combination of AET and mexamine was confirmed by A. V. Bogatyrev [457].

The significant toxicity, also serving as the cause of death of individual animals (see Table 25) is the substantial deficiency of the complex of protectors used. For the purpose of eliminating the toxicity the mixture ratio and the doses of its components were changed. The lowering of the dose of mexamine was validated based on the data about the preservation of its pharmacological and anti-radiation activity within rather wide limits (30).[1] The decrease in

[1]R. B. Strelkov [868] established the steady effect of mexamine on mice at doses of 7.5-1.50 mg/kg upon subcutaneous introduction (35-50% survival with 100% death of the animals in the control, γ-quantum Co^{60}, 900 R).

B. Karochkin and G. M. Ayrapet'yan together with us obtained data about the effectiveness of small quantities of mexamine on mice (7.5-30 and 15-75 mg/kg by intraperitoneal and oral means of introduction, respectively). However, in contrast with the data from R. B. Strelkov we established (using a powerful source of γ-radiation of Cs^{137} – GUPOS*, 710 r/min) that the degree and duration of the protective effect strongly depend on the amount of preparation both at the marrow, and in the intestinal syndrome.

*[Translator's note: Unidentified abbreviation. The first three letters suggests that it is related to a gamma-radiation source measurement].

the number of AET was proposed to compensate for the additional introduction into the composition of the complex less toxic thiol-cystaphos. The results of experiments based on the test of the formulated complex (Table 26) made it possible to note two important facts. In the first place, despite the sharply reduced numbers of all three components (AET by 6, mexamine by 3 and cystaphos by 2 times), the antiradiation activity of the complex was rather high. At a dose of 1100 rads the utilization of the complex controlled 52% survival of the animals (FUD ≈ 2) and considerably increased the duration of life (from 4.6 to 10.3 twenty-four hour periods). In the second place, in the combined utilization of protectors at such small doses the criteria of the toxic effect was not observed.

Table 26. Effect of the complex of protectors on the survival of mice, subjected to X-ray irradiation at a dose of 1100 rads (intraperitoneal injection for 10 min prior to irradiation).

Preparation μ/kg as a base	Number of mice	Survival at the 30th twenty-four hour period		Average duration of life, twenty-four hour periods
		Number	%	
Physiological solution, 0.2 ml.....	20	0	0	4.6
Mexamine, 25 + AET, 25 + cystaphos, 175	40	21	52.5	10.3

High effectiveness of the given complex of protectors was confirmed by G. M. Ayrapet'yan in an experiment on mice (Table 27) which is reflected both on the survival, and on the duration of life of the animals, as evidenced in the protection not only in the bone marrow but also in the intestines.

Table 27. Effect of the complex of protectors on the survival of rats subjected to X-ray irradiation at a dose of 1100 rads (intraperitoneal injection for 15 min prior to irradiation).

Protector, mg/kg as a base	Number of rats	Number of animals, survived at the 30th twenty-four hour period	Average duration of life, twenty-four hour period
Physiological solution, 1 ml.....	10	0	4.7
Mexamine, 5 + AET, 20 + + cystaphos, 175.....	10	5	12.6
Mexamine, 5 + AET, 50 + + cystaphos, 250.....	10	10	–

The Combined Application of Protectors with Fractionated Irradiation

Conducting analogous experiments under conditions of repeated pressure served as a basis for the possibility of an increase in FUD by the combined application of protectors with a single exposure.

As can be seen from Table 28, the application of the previously described complex of cystaphos with mexamine [387], conditioned the high protective effect at repeated irradiations at supralethal doses (950 rads) at an interval of 30 days [383].

The combined application of the same protectors managed also to substantially raise the survival of the mice at a quadruple irradiation at a dose of 400 rads with 5 twenty-four hour intervals (Table 29), i.e., under conditions, when the individual introduction of compounds seems slightly effective or entirely ineffective (Fig. 29).

The results of the experiment on test of another complex (mexamine + AET + cystaphos) with quadruple irradiation of mice at a dose of 300 rads with intervals of 2 twenty-four hour periods are very indicative. As can be seen from Table 30, the simultaneous application of protectors in small doses was accompanied by expressed potential effect, as a result of which only one of the 30 experimental animals perished with 90% mortality in the control.

Table 28. Survival of mice with double repeated irradiation at a dose of 950 rads with 30 twenty-four hour intervals under conditions of combined protection (intraperitoneal injection for 10 min prior to irradiation).

Protector, mg/mouse	1st irradiation		2nd irradiation	
	Number of mice	Survival, %	Number of mice	Survival, %
Physiological solution, 0.2 ml (control).....	0/20	0	–	–
Cystaphos, 7.....	7/20	35	2/7	28
Mexamine, 1.5.....	3/20	15	0/3	–
Cystaphos, 7 + mexamine, 1.5.....	36/40	90	32/36	88.8

Note. In the numerator – number of survived mice at the 30th twenty-four hour period following irradiation, in the denominator – the number of animals, introduced into the experiment.

Table 29. Survival of mice, subjected to fractionated irradiation (400 rads 4 times over 5 twenty-four hour periods) during combined and individual application of the protectors.

Protector, mg/mouse	Number of mice	Survived at the 30th twenty-four hour period following the last irradiation	
		Number	%
Physiological solution, 0.2 ml control).....	30	0	0
Mexamine, 1.8.....	30	3	10	
Cystaphos, 7.....	30	1	3.3
Mexamine, 1.8 + cystaphos, 7.....	60	36	60.0

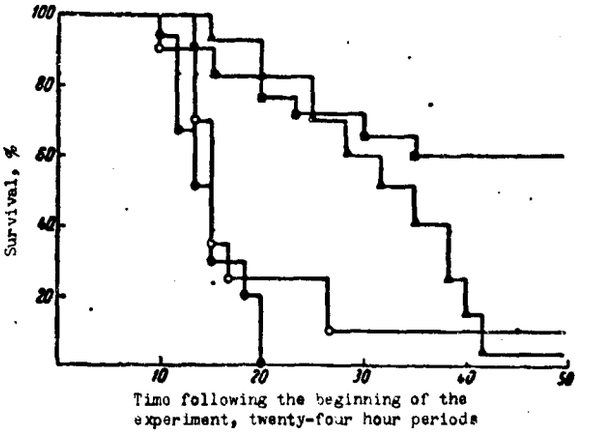

Fig. 29. Survival of mice with fractionated irradiation (400 rads × 4 times through 5 twenty-four hour periods) under conditions of protection: ● – control; O – mexamine; ▲ – cystaphos; ■ – complex.

Table 30. Effect of the radioprotective complex on the survival of mice with quadruple irradiation at a dose of 300 rads with two twenty-four hour periods.

Protector, mg/kg	Number of mice	Survived at the 30th twenty-four hour period	
		Number	%
Physiological solution, 0.2 ml.....	20	2	10
Mexamine, 25 + AET, 25 + + cystaphos, 175.....	30	29	97

An increase in the protective effect in the combined application of protectors under conditions of repeated irradiation both at the supra-, and at the sublethal doses can be governed primarily by the intensification of the protection of the bone marrow. The results of corresponding experiments confirmed such an assumption.

The data described in Chapter IV about the dynamics of karyocytes in the bone marrow of the femur of mice on the 3rd twenty-four hour

period following X-ray irradiation at doses of 300, 400, 600 and 900 rads under the effect of individual application of cystaphos, mexamine and their complex, have been partially reproduced in Fig. 30.

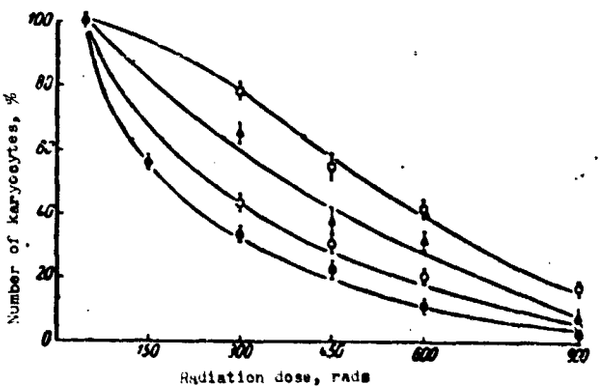

Fig. 30. The number of karyocytes in the bone marrow in the femur of a mouse at the 3rd twenty-four hour period following irradiation in different doses under the effect of individual protectors and their complexes: ● – control; ○ – cystaphos; ▲ – mexamine; □ – complex.

FUD based on this criterion over the range of 300-600 rads is approximately equal to: 1. 2 and 3, respectively, for cystaphos, mexamine and their complex; only at a dose of 900 rads the amount of FUD is noticeably reduced: it is less than 1.5 for each of the protectors and less than 2 for their complex.

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At the same time, following from Fig. 30, with the lowering of the dose of irradiation the portion of protected cells with the complex and as a whole number of the cells is diminished and preserved at the given dose. The number of K (see Chapter IV) at doses of 900, 600, 450 and 300 rads comprise 0.75; 0.68; 0.58; 0.56, respectively. Consequently, the relative value of protected cells is also diminished which obviously also explains the lowering of the coefficient of protection based on the test of survival.

The substantial increase in the survival under the effect of the shown complex was also observed with double X-ray irradiation at doses of 500 and 600 rads at an interval of 1 twenty-four hour period (Table 31).

Table 31. Survival of mice with double irradiation in doses of 500 and 600 rads with a twenty-four hour interval under conditions of separate and combined application of protectors (intraperitoneal injection for 10 min prior to each irradiation).

Protector	Number of mice	Survived at the 30th twenty-four hour period		Average duration of life, twenty-four hour periods
		Number	%	
Control.....	20	0	0	8.4
Mexamine.....	30	8	25.6	10.6
Cystamhos.....	30	11	36.6	13.8
Complex.....	60	41	68.8	16.0

In this instance, despite the large cumulative dose (1100 rads), the protective effect of mexamine was revealed, which, as shown above, did not protect against the intestinal form of death. This was possible due to the peculiar epithelium of the intestinal crypt of high mitotic activity and associated with its intensive reparation, the manifestation of which, as was shown by G. S. Strelin and K. P. Calkovskiy [458], sharply facilitating it with the lowering of the dose rate, and in our attempts at its fractionating.

In connection with this, favorable conditions were formed for the manifestation of the unique complex in the magnitude of FUD in relationship to bone marrow which is also expressed in the average of survival by 30-40% in comparison with the effect of the separate introduction of protectors and the double increase in average duration of life of animals in comparison with the control (see Table 31).

The determining role with respect to the effect of the protection of the amount of FUD over a considerable radiation dosage and beyond the dependence on preliminary reduction action was also

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confirmed in experiments with the combined application of preparations in the process of irradiation [372, 373], conducted according to methods described in Chapter IV.

After administering doses of 150, 300 or 450 rads, the irradiation was interrupted, the animal received a mixture of protectors and for a period of 15 min irradiation was continued at doses of 850, 570 and 285 rads, respectively. With the allowance for a FUD = 1.9 the expected cumulative dose in all three cases should amount to 600 rads, i.e., approximately LD_{50}. As seen from Fig. 31, the proposed protective effect and that observed in the experiments differed little, despite the fact that the protectors were applied over a range of doses of 285-850 rads on a background of preliminary irradiation at doses of 450-150 rads. In all three variants of experiments, at the 30th twenty-four hour period about one-half of the protected animals survived.

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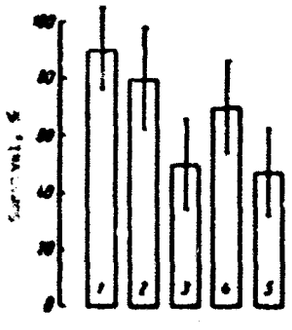

Fig. 31. Survival of mice upon the introduction of protectors in process of irradiation. (Reliable intervals with R < 0.05): 1 – complex + 950 rads; 2 – complex + 300 rads + 650 rads; 3 – 150 rads + complex + 850 rads; 4 – 300 rads + complex + 570 rads; 5 – 450 rads + complex + 285 rads.

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Thus, in the experiment the predicted amount of FUD was confirmed theoretically for complex, which was accepted at all radiation doses equal to 1.9 (on the basis of experiments with lethal irradiation). Therefore, sum total effect of irradiation (with the allowance for protection) was close to that expected (Fig. 32).

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Thus, the combined application of protectors with repeated irradiations governed the substantial increase in the survival of

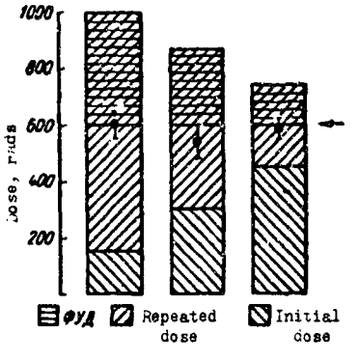

Fig. 32. Expected degree of injury using the sum total doses with the allowance for the amount of FUD, equal to 1.9, (shown by the arrow) and that the actually obtained in experiments (experimental points and reliable intervals with R < 0.05).

the animals, associated primarily with the increase in the amount of FUD in relationship to the bone marrow over the range of sublethal, lethal and supralethal doses.

Analysis of the Possible Mechanisms of Combined Protection

The basic goal of the experiments, the results of which were presented in this chapter, – to study the possibility of the intensification of the protective effect with single and fractionated irradiation by means of the combined application of protectors. The given data uniquely provides evidence of the fact that the complex of aminothiols and indolylalkylamines is a very promising combination. Specifically, during the simultaneous application of optimum doses of MEA or cystaphos with mexamine, synergism is observed in the action of the shown protectors, owing to the fact that the FUD complex increases approximately up to 1.9 in comparison with 1.5 during their separate application.

The combined application of AET and mexamine or its combination with cystaphos not only causes a synergistic effect, but also a potentiating effect. In this instance, FUD attains the same magnitude with the application of doses of protectors which amount to 1/2-1/6 of the optimum. By example, a formula comprising mexamine, AET and cystaphos (respectively, 25; 25 and 175 mg/kg), and which contains 1/3 of the optimum dose of mexamine and 1/4 of the potential

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mercaptoethylamine can serve as such a complex. Separate application of thiol protectors in the shown amounts is practically ineffective even at moderately lethal doses, while the complex governs the survival of one-half of the animals, irradiated at a supralethal dose of 1100 rads. The effectiveness of the complex application of aminothiols and indolylalkylamines, simultaneously or independent of us, was also confirmed by other researchers in experiments on mice and rats [156, 408, 409, 414, 417, 453, 455, 459-462], dogs [387] and monkeys [463].

Earlier the two most valid assumptions were mentioned about the nature of synergism of the shown protectors, for which there are determined experimental data.

According to one of them, the intensification of the protective effect was associated with various mechanism of effect of aminothiols and indolylalkylamines [438-441], in that the first ones carry out protection in an oxygen-independent way, and the second ones – owing to hypoxia. This point of sight, despite its attractiveness as a whole, was vulnerable from positions of the unitary mechanism of protection [7, 94, 159-161].

More probable, but not exclusive of the first, one ought to recognize the second assumption, based upon the possibility of the differentiated protection of different systems, primarily the bone marrow and intestines. Besides this experimental evidence of the validity of such a conclusion, the favorable effect of the restoration of hemopoiesis for protecting the intestines gives evidence [464], which is accompanied by the intensification of mitotic activity of the bone marrow. In fact, this is also the basic reason for the protective effect, since metaplasia of the lymphoid elements, as special investigations [465] have showed, is excluded.

What is the reason for this phenomenon? What is the connection between the protection of the intestines and the activation of mitoses in the bone marrow?

It is possible that the mechanism of intensification of the reparation in this case has a predominantly genetic nature and consists of supplying progenic precursors of dioxyoribonucleic acid [DNK] (ДНК) from the protected section of the intestines in the bone marrow.

As the cytogenetic analysis showed, as a result of the irradiations, the corresponding function of the bone marrow is suppressed [466]. The results of experiments with ascitic cells of Erlich's carcinoma having shown more value for the restoration of their viability following irradiation than the phenomenon of cellular interaction, including the transfer of fractions of nuclear matter from the nonirradiated cells to the irradiated ones [467], correspond to this hypothesis. It is possible that the weakening of the aplasia of the bone marrow under the effect of the complex in comparison with the separate application of protectors (see Fig. 30) to a known degree has the same character due to the protection of the intestines.

Clear synergism, disclosed with the complex application of small doses of protectors, can explain the intensification of the pharmacological effect of mexamine under the effect of AET [32], as a result of which a spasm of the vessels of the mesentery appears. It is curious that during the attempt at a combined application of AET and mexamine, P. G. Zherebchenko [32] also detected the high toxicity of this complex. In order to weaken it, the amount of mexamine (up to 5 mg/kg) was lowered; in this case a high radioprotective effect (68% survival in irradiation at a dose of 1200 R) was observed.

The extremely important possibility, in principle, of increasing the protective effect without a noticeable toxic manifestation represents the practical aspect. In contrast with the previous data whereby it is impossible to use AET on dogs because of its toxicity [468], recently data were received about the high effectiveness of complex AET with para-aminopropiophenone for this species of animals not only by parenteral introduction, but by oral introduction [392, 435, 436] as well.

No less fundamental is the conclusion about the fact that the combined application of protectors seems effective over a wide range of moderately lethal and supralethal doses not just with single irradiation but also with fractionated irradiation and during the process of radiation exposure.[1] Under the effect of the complex a considerable increase in the survival of such variants of fractionating, when the separate application of the protectors is not effective, is observed.

Independent of us, the effectiveness of the complex application using serotonin, AET and MEA with repeated irradiations on mice at supralethal doses [470] was shown. Unfortunately, the authors could not avoid the manifestations of toxicity in connection with the application of large doses of preparations. But, in another investigation the high antiradiation effect was detected with repeated irradiation on dogs at sublethal single doses (200 R) with the application of reduced nontoxic amounts of AET and para-aminopropiophenone [392]. In these experiments the control animals perished at a cumulative dose of 866 R, and the protected ones at 3550 R.

Thus, the earlier made conclusion about the deciding role in the outcome of pro ection of both the single, and repeated irradiation of protectors with an actual amount of FUD is confirmed.

Conclusion

The combined application of aminothiols and indolylalkylamines in conventional or reduced doses leads to a considerable intensification of the protective effect. This manifests itself by the increase in the survival of animals (increase of FUD up to 1.9 in comparison with 1.5 using separate application of protectors) even during the change in the amount of karyocytes in the bone marrow (the number of FUD are respectively, equal to 3 and 1.5-2).

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[1]The data on the effectiveness of protectors during their application during the process of irradiation were confirmed in experiments on mice, subjected to γ-radiation under a condition, simulating solar flare [469].

The differentiated protection of the radiosensitive systems, the different mechanism of effect of individual protectors at the cellular level and the intensification of thiols (especially AET) of the pharmacological effect of indolylalkylamines are the basis of synergism and potentiation of the effect of the studied compounds.

The effectiveness of the complexes of protectors seems to be expressed to an equal degree over a considerable range of the sub-, moderate- and supralethal doses both with single and with fractionated irradiation.

The obtained data support the formulated presentations about the increase in radioresistance of an organism under the effect of protectors as a result of the favorable conditions for regeneration as a result of the preservation of a large part of the unimpaired cellular elements in the critical radiosensitive organs in accordance with the overall behavior of their post-radiation reparation, established by G. S. Strelin and coworkers [399, 458, 471-476].

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CHAPTER VI

POSTRADIATION RESTORATION ON AN ORGANISM UNDER VARIOUS CONDITIONS OF IRRADIATION

The basis of the previous examined restorative processes in an irradiated organism rests on the postradiation of the cellular population due to undamaged or protected cellular elements. The level and the rate of restoration, therefore, are determined primarily by the radiation dose or by the degree of protective effect and correspondingly, by the number of preserved cells – a kind with a background of subsequent regeneration.

In principle, another method of postradiation reparation consists of the restoration of the viability of the damaged cells themselves, specifically, their chromosomal complex, whose radiation damage until recently was ascribed as an irreversible pattern. However, convincing material is accumulating, which testifies to the reality of postradiation restoration of damaged biological structures at the various levels of vital organization [477-479].

As the basis for the development of these investigations, one ought to consider the expressed assumption by Svenson about the fact under the effect of ionizing radiation not only true mutations appear, but also the so-called potential changes representing some metastable state, which, depending on conditions, is either restored to its original structure, or will be realized through mutation [480].

It was established that the increases in the survival of bacteria [481] parameqil [482] tumoral [482a] or isolated yeast cells [478,

479, 483] can succeed in changing the conditions of their postradiation culture, and in the culture of animal cells – by repeated irradiation through definite intervals [484-486]. Fact of the restoration of cells from damage causing chromosomal aberation on vegetative media, was established by N. V. Luchnik and coworkers [296, 487-490]. In experiments on wine flies [491] and mice [492] the restoration of the sexual cells from damage causing lethal mutation was shown. Together with G. F. Palyga and I. M. Shapiro, we established the reparation of chromosomes in quiescent cells of the liver with the lowering of the dose rate of irradiation [25, 493, 494], but recently in intrinsic experiments the possibility of postradiation restoration of an organism was shown [372, 495, 496], which can be explained by the restoration of viability in a part of the cells of bone marrow and intestines.

At the same time one ought to recognize that the mechanism of postradiation restoration of cells and of their structual elements has been insufficiently clarified.

In the majority of works the survival of cells or genetic changes has served as the criterion of restoration. It was established that the factors, which prevent the reunification of chromosomal ruptures induced by irradiation, result in an increase in the number of overmaturing ones. Thus, if during the period of irradiation, the buds of Tradescantia are subjected to centrifuging, then number of structural changes is increased [497]. Centrifuging did not affect the number of chromatidal and chromosomal exchanges, if it was conducted over a period of 5 min following irradiation; obviously, during this time the lacerated chromosomes succeeded in uniting and additional exposures were futile.

During the irradiation of onion rootlets, treated with colchicine at a dose of 300 R, the number of chromatidal aberrations was 3 times less than in rootlets, irradiated without the preliminary treatment; this is associated with deceleration of the motion of chromosomes in th rophase under the effect of colchicine favorable to the restoration of the structure [498].

The decrease in the number of aberrant cells in the rootlets of a pea in proportion to the length of time of the introduction of cells during mitosis following irradiation also can be explained by the postradiation restoration, carried out during the interval of time between irradiation and the onset of division [296, 488-490].

A series of investigations was devoted to the effect of oxygen on the process of incurring chromosomal damage. It was shown that the ruptures of the chromosomes, appearing during the irradiation in presence of oxygen, remain open for about 2 h [499, 500]. This time was considerably shortened by the treatment of seeds with 2, 3-dimercaptopropanol at the end of moistening, and likewise the number of double-nucleus aberrations is reduced. An analogous effect was observed during the irradiation in a vacuum.

During the sprouting of barley seeds soon after irradiation at doses of 45 and 90 R, the number of cells with aberrations was small in comparison with the control. During long storage, especially in the presence of oxygen, it was considerably increased, and incubation in nitrogen weakened the postradiation changes [501, 502].

Oxygen facilitated the passage of latent breakdowns, or potential ruptures [480], and in fact, conversely, in the absence of oxygen the restoration of cells increased [503]. The treatment of barley seeds with oxygen right after irradiation intensified their radiation damage [504, 505]. If the barley seeds or cells of Erlich's ascitic carcinoma were held in vacuum for 2 h following irradiation, then the number of chromosomal breakdowns was reduced [505].

A detailed examination of the contemporary state of the problem about postradiation restoration was carried out by V. I. Korogodin [478, 479] and N. V. Luchnik [506]. This made it possible to limit the given works to a brief summary from which it is evident that the radiation damage of the cells is not always the irreversible result of elementary ionization actions and can be modified during the postradiation period. Below certain experimental data will be examined with an attempt of an analysis of the connection between

antiradiation protection and postradiation restoration.

The Effect of Local Anoxia on the Reaction of Radiation After-Effect in Bone Marrow

Majority of works on the analysis of oxygen after-effect were done in model systems at molecular and cellular levels. The results of experiments, conducted at a level of an organism, are ambiguous [507] and they require further development.

For the clarification of the role of local anoxia of the bone marrow during the postradiation period on both femurs of mice for 5-10 min prior to overall irradiation at a dose of 700 rads, ligature was employed. From one extremity right after irradiation the ligature was removed, and to the other, it was held for 20 min more [508]. The presence of the oxygen after-effect was ascertained from the results of the cytological analysis of the bone marrow.

The data in Table 32 bears evidence of the indubitable effect of oxygen after-effect, which continues following the irradiation by a state of anoxia of bone marrow and which consists of a decrease in the cellular degeneration in the experimental extremity by 25% in comparison with the control.

Table 32. Degeneration of the cells of bone marrow through 4 h following overall irradiation of mice at a dose of 700 rads (results of research on 96 preparations from 32 animals).

Extremity of the animals	Time of removal of the ligature	Number of degenerative nuclei, %	T
Control	Right after irradiation. .	100	5.2
Experimental	Through 20 min following irradiation.	75	

Postradiation effect of anoxia also affected the processes

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of restoration – in the form of the intensification of the mitotic activity and the reduction of the number of cells with chromosomal aberrations (Table 33 and 34). Although the differences with the control, as statistical treatment have shown, are unauthentic, nevertheless the excess of mitotic activity in the experimental extremity over the control was observed in 12 of 15 mice.[1]

Research of the effect of the time factor on the antiradiation effect of local [illegible] disclosed that ligature applied for 2 h, intensifies the radiation degenerative changes in the cells of bone marrow. As was explained in experiments on intact animals, the application of the ligature for itself 1 h and more causes cellular degeneration, which is revealed only at a certain later time (not less than 1 h) following the removal of the tourniquet. This delay in the manifestation of the shown changes in equal regularity is characteristic both for the intact and for the irradiated animals. In the opinion of N. F. Barakin [264, 265], who observed analogous phenomenon by applying ligature to the vascular leg of the spleen, the morphological changes in cells proceed immediately following irradiation, but they manifest themselves only after the union with the organism is restored.

Thus, mammals also have shown the possibility of modifying radiation damage during the postradiation period by means of temporary stopping of oxygen access to the section of the irradiated bone marrow.

Relative to the mechanism, the realization of the oxygen after-effect has gained no unaminous opinion. In accordance with the

[1]The experimental data was obtained in 1959 and, unfortunately, may not completely characterize the studied phenomenon, because the estimate of mitotic activity and the analysis of chromosomal damages were performed only during one period (5 twenty-four hour periods following irradiation). Recently V. I. Korogodin cordially reported to us about the fact that, according to the observations in his laboratory, the application of the ligature following irradiation facilitated the intensification of mitotic activity of the bone marrow, most distinctly manifested at the 10th twenty-four hour period following irradiation.

Table 33. Mitotic activity of hemopoietic cells of mice through 5 days following overall irradiation at a dose of 700 R (data obtained on 15 animals).

Group	Type of tissue	Time of removal of the ligature	Number of counted cells		Mitotic index, ‰	T
			Whole	Dividing from them		
Experiment	Bone marrow from the shin bone	Through 20 min following irradiation	22,000	817	3.7±0.2	1.8
	The same one	Right after irradiation	21,000	674	3.2±0.2	
Control	Bone marrow from the breastbone	–	Marked depletion by hemopoietic cells		0–1.0	–
	Spleen Thymus	– –	Individual mitoses in the preparation against a background by cutting the cellular aplasia.			

Howard-Flanders hypothesis, oxygen effect is caused by the competition of oxygen and thiol protectors – donors of hydrogen – for latent damage, which appear in the biological macromolecules [509]. Reparation is observed from the interaction of the damaged molecules with hydrogen, and realization of injury goes on in the case when molecules unite with oxygen.

Recently, based on model experiments of I. Kh. Eydus [510] the conclusion was drawn that the realization of the oxygen effect

Table 34. Chromosomal aberrations in the bone marrow of mice on the 5th twenty-four hour period following overall irradiation at a dose of 700 rads (the data obtained on 20 animals).

Time of removal of the ligature	Number of studied mitoses (ana-and telephases)			Number of chromosomal aberrations, %	T
	whole	normal	damage		
Through 20 min following irradiation (experiment).	3800	3315	485	13.1±0.8	2.3
Right after irradiation (control) . . .	4200	3539	661	16.1±0.8	–

proceeds in another way. With indirect radiation effects the OH• radicals, generating as a result of the radiolysis of water, strike, bilogically important macromolecules, inflicting latent damage in them. If in the solution, apart from the macromolecules, low molecular impurities are found, then the water radicals can intercept them with the formation of radicals of the impurities. Latent damage to the macromolecules prior to their realization as evident damage under the effect of various physical factors, specifically oxygen, can be reparable with the interaction of radicals of certain impurities, for example thiol protectors. Oxygen, present in the medium during irradiation, with the interaction of radicals of impurities, inactivates them, i.e., deprives them of the ability to repair the latent damage of the macromolecules. Consequently, in the opinion of L. Kh. Eydus, the effect of all protectors amounts to the fact that their radicals are capable of repairing latent damage even prior to its realization under the effect of oxygen. Both the Howard-Flander's, and L. Kh. Eydus's hypotheses can be fully extended beyond the point of a model experiment. It is known that in solutions, the various low molecular impurities are able to lower the radiation damage of the substratum whereas for organism the strict specificity of protectors is characteristic, which cannot be elucidated from these positions. In contrast with

model experiments at the molecular level, in which the oxygen after-effect constitutes a considerable portion of the overall damaging effect [511], in the organism, role of oxygen pre-damage, obviously, is modest. In special experiments we could not detect how substantial was the increase in the survival of mice using ligature, applied for 20 min following irradiation, in comparison with animals, in which it was removed simultaneously with the termination of exposure. Not withstanding, this is associated only with the insignificant portions of additional protection of a section of the bone marrow, since the content in guinea pigs following irradiation in an atmosphere of CO facilitated an increase in their survival [512].

The obtained data can introduce certain corrections in the presentation about the mechanism of effect of protectors of the "hypoxia" type, since the time of their effectiveness, not being limiting by a period of exchange of radiation energy, occupies a certain interval even following irradiation. In this light there exists the known explanation of Langendorf's communication with his coworkers, [326] about the effectiveness of serctonin upon injection immediately following irradiation; but, unfortunately, it still is not confirmed by other researchers.

One ought to keep in mind that the presence or absence of the oxygen after-effect, just as with temperature, can determine not just the conditions and characteristics of the experiment. For example, according to I. B. Bychkovskaya, under the same conditions of a content (+3 and +5°C), the oxygen after-effect was observed in a fr[illegible] [513] and was absent in granary weevils [507].

Reparation of Chromosomal Damage with Chronic Exposure

Along with the data about the reality of postradiation restoration of genetic structures, produced on media characterized by a high level of cellular division, there is information on the "preservation" of structural damage of chromosomes in eggs of silkworm [514], cornea of frog [513], liver of mice and rats [515-518]. In accordance with the data of I. M. Shapiro, the portion of cells of the liver

with chromosomal aberrations, appearing after a single overall X-ray irradiation, does not change over a prolonged period (2-4 months). With a fractionating dose (2 times at 250 rads with an interval of 7 twenty-four hour periods) effect is summarized and is equivalent to that observed with a single exposure at a dose of 500 rads [515].

It was necessary to explain, to what degree the chromosomal defects are retained in the cells of the same liver with chronic exposure. In other words, whether or not the process of mutation in somatical cells of mammals depends on the dose rate similarly, as the most varied polyclinical manifestations of radial injury depend, the degree of which is considerably weakened with the protraction of radiation exposure with time.

Research of this phenomenon is important not only for an understanding of the mechanism of radiation damage of chromosomes, but also for an estimate of the remote consequences of irradiation, and also as a basis of hygienic standardization of the radiation factor. For this purpose a corresponding experimental investigation on white male rats weighing 160-180 g [25, 493, 494], was made.

It is known that in cells of the liver of adult rats, the mitoses are very rare: one per 10-20 thousand cells [519]. With the help of a partial hepatectomy it is possible to cause a sharp intensification of the mitotic activity of the cells in the constricted part of the organ. Thus the liver – convenient and unique specimen for research on a number of processes, taking place in the interkinesis over a prolonged interval, with the subsequent analysis by means of stimulating the cells into division. After a partial resection of the liver, regeneration does not take place in the usual sense of the word, i.e., forming the lacking parts of the organ again, but the intensified division of the cells in all parts of the organ [520], are observed, hypertrophy of the lobule [521] and polyploidy of the cells [522].

Experimental animals were subjected to γ-irradiation with a cumulative dose of 150 rads at a different dose rate. The strength

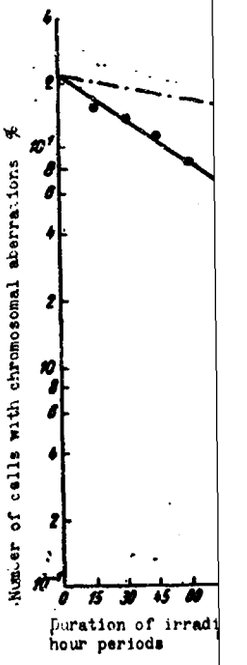
of the dose was selected for the purpose of preferential injury of one chromosome in the cells. As shown in [516], this can be expected: such a injury was approximately allowed with X-ray irradiation at a dose of 92 R. Taking into account an relative biological effectiveness [OBE] (ОБЭ) of γ – radiation Co^{60}, equal to approximately 0.6-0.8, we will obtain about 150 R.

Hepatectomy based on the standard method [186] is always produced in the morning, taking into account the data from L. D. Liozner and coworkers [538], which has shown that for rats treated in the morning hours the total sum of cells in state of mitosis, is detectable at various times of a twenty-four hour period, more so than during night treatment. Thus, the elimination itself of the damaged cells was facilitated which satisfied our interests (one has in mind the high assurance in the conclusions relative to the possible weakening of the radiation effect).

For the intact control rats with a weight of 160-180 g 6.9±0.3% cells of the liver with chromosomal aberrations was counted. With the increase in number they increased up to 8.1±0.6% over 3 months following the beginning of the experiments and up to 11.6±0.4% over 6 months (Table 35). For the experimental animals in proportion to the reduction of the dose rate, the number of cells with chromosomal damage was diminished, and during irradiation for 6 months (dose rate of 0.58 × 10 rad/min) was not distinguishable from the control.

Dependence of the dynamics of cells with chromosomal damage induced by irradiation on the duration of exposure, is exponential (Fig. 33).[1]

The decrease in the effect with an increase in the duration of irradiation can be explained:



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[1]For the determination of chromosomal damage induced by irradiation the data about the number of cells with aberrations during corresponding periods in the control is deducted from the data, obtained in the experimental animals.

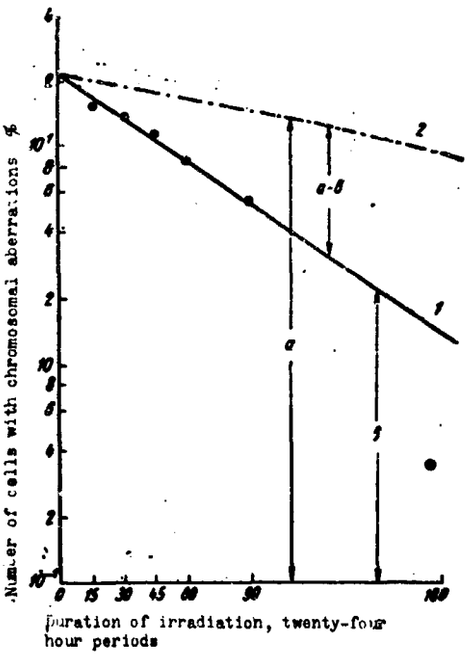

Fig. 33. Change in the number of cells with chromosomal aberrations depending upon the duration of irradiation. Shown in the figure is the expected number of cells with chromosomal aberrations taking into account their possible elimination during division (a) and observable number of cells with aberrations (b), and likewise the effect of the reparation of chromosomes (a-b): 1 – experimental data; 2 – calculation data.

Table 35. Content of cells with chromosomal aberrations in the liver of rats following overall γ – irradiation of Co^{60} at a dose of 150 rads.

Index	Duration of irradiation (twenty-four hour periods) at a dose rate, rad/min						
	Single, 26	15, $7 \cdot 10^{-3}$	30, $3.5 \cdot 10^{-3}$	45, $2.3 \cdot 10^{-3}$	60, $1.7 \cdot 10^{-3}$	90, $1.15 \cdot 10^{-3}$	180, $0.58 \cdot 10^{-3}$
Control							
Number of cells with aberrations, %.	29,3±1,1	21,8±0,7	21,2±1.2	19,2±0,8	16,2±0,5	13,9±0,5	11,8±0,6
Number of cells with aberration, induced by irradiation, %.	22,4	15,3	14,0	11,5	8,7	5,8	0,2
Number of animals.	6	6	6	8	6	9	8
Experiment							
Number of cells with aberrations, %.	6,9±0,3	6,5±0,6	7,2±0,5	7,7±0,5	7,8±0,5	8,1±0,6	11,6±0,4
Number of animals	20	6	6	6	6	8	7

1) elimination of cells with chromosomal aberrations during the process or following the division;

2) selective death of the cells with chromosomal aberrations during the interphase;

3) weakening of the primary radiation effect or by the restoration of chromosomal structure.

Let us analyze in sequence all three of the shown possibilities.

According to the mentioned data [519], mitotic index in the liver of adult rats constitutes 0.01-0.005%. Recently, information appeared on the higher rate of physiological generation of the liver of rats weighing 160-180 g, as a result of twenty-four hour periodicity of mitoses [523] with an average twenty-four hour period of mitotic activity up to 0.1% [524]. During the count of 100,000 of the liver cells of the control of unirradiated animals used in our work, the mitotic index during the morning hours, when the acitivity was maximum [524], was equal to 0.0048%, and over 24 h after a single γ-irradiation at a dose of 150 rads – 0.0057%. According to finnish researchers [525], a single X-ray irradiation at a dose of 250 R likewise did not affect the rate of division of the cells in the normal liver of rats. There is every reason to suppose that the mitotic activity using chronic exposure with a different intensity at a cumulative dose of 150 rads should not be substantially distinguished from the norma. Assuming that it, in this instance, is equal to 0.0067% (or 1:15,000, i.e., even higher than that observed in the experiments, and that the duration of mitosis is equal to 30 min [526, 527], it is possible to calculate, the number of liver cells that will participate in the investigated periods. For example, if the duration of irradiation is equivalent to 180 twenty-four hour periods, and for 30 min, division takes place in 0.0067% of the cells of the liver, then 57.6% of the cells will participate to the termination of the irradiation. Even when based on the known improbable assumption that only the cells with chromosomal damage underwent division, then to be completely equal as a result of their elimination 9.6% of the cells with

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aberrations in comparison with 22.4% of those observed following single γ-irradiations of Co^{60} at a dose of 150 rads, should remain. Following from the given data, after 6 months of radiation exposure at a dose rate of $0.58 \cdot 10^{-3}$ rad/min only 0.2% cells with chromosomal rupture, induced by irradiation (see Table 35), appeared. If the diminution of cells with aberrations were caused only by their death during or following division, then the dependence of the number of damaged cells on the duration of irradiation would have the form of a straight line 2 in Fig. 33. As it appears, expected (curve 2) and observed (curve 1) of the dependence substantially diverge. Consequently, in order to explain the observed reduction in the number of cells of liver with chromosomal aberrations solely by their elimination as a result of division is impossible.[1]

The assumption about the interphased death of cells also is highly improbable, inasmuch as the cells of the liver of rats are very radioresistant and do not perish during the interphase even following exposure at considerable stronger doses [360]. Furthermore, as shown in the example of cells of the bone marrow or the crypt of the intestines, interphasal death, apparently, is not associated with chromosomal aberrations [528, 529].

Thus, it is necessary to admit that the observed dependence of the reduction in the number of cells following chromosomal damage on the duration of irradiation and on the dose rate can explain the true reduction of the radiation effect, possibly, as a result of the restoration of the structure of chromosomes, i.e., by their reparation from the damage.

During the examined effect the preferential value, apparently, possesses a dose rate, but not with time, during which the cells exist during the interphase following irradiation.

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[1]This conclusion becomes even more convincing, if one considers that according to other data, the mitosis of the cells of the liver of rats continues for more than 100 min (Post, I., Hoffman, J., Explt. Cell. Res., 36, III (1964); sitation in [519]), i.e., the time is three times longer than what we have accepted.

Results of chronic exposure of rats for 15 twenty-four hour periods (Table 36) are evidence of such a conclusion. Through 24 h following the termination of exposure 21.8±0.7% of the cells with chromosomal aberrations (in the control animals, a corresponding increase of 6.5±0.6%), and through 5.5 months – 23.0±0.8% (in the control, 11.6±0.4%) was detected. A certain decrease in the manner of aberrant cells through 5.5 months can be explained by their partial elimination as a result of division. These data at one time confirmed the ability of the cells of the liver to retain the damage of chromosomes following a single γ-irradiations [515-518, 530] for a long time during the interphase.[1]

Table 36. Preservation of chromosomal damage in the cells of the liver of rats after 15 twenty-four hour periods of chronic γ-irradiation of Co^{60} with a cumulative dose of 150 rads with a dose rate of $7 \cdot 10^{-3}$ rad/min.

Experimental scheme	Group	Number of animals	Number of cells with chromosomal aberrations, %	Number of cells with chromosomal aberrations, induced by irradiation, %
Chronic exposure, hepatectomy over 24 h	Experiment	6	21.8±0.7	15.3
	Control	6	6.5±0.6	
Chronic exposure, hepatectomy 5.5 months	Experiment	5	23.0±0.8	12.4
	Control	7	11.6±0.4	

[1]Data on the long (6 months) preservation of cells with chromosomal aberrations reject the assumptions about the possible complete auto-restoration of cells of the liver [519], taking place in rats allegedly for 40 twenty-four hour periods [523]. Obviously, the observed mitotic activity as a standard is peculiar only to definite types of cells of the liver, most likely, of the Kupffer type.

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Below, are given the quantitative characteristics of the effect of reparation of chromosomes during the interphase of cells in the liver [494].

In the absence of division the number of cells of the liver with chromosomal aberrations A_0 will constitute 22.4% (effect of a single exposure without a background) after the accumulation of dose $D_{\text{макс}}$ for T days. Assuming that the division of the cells of the liver with aberrations and without them it is equally probable, then the increase in the number of cells with aberrations can be calculated by the formula

$$\frac{dA}{dT} = k\frac{D_{\text{макс}}}{T}(1-A) - qA = k\frac{D_{\text{макс}}}{T} - \left(k\frac{D_{\text{макс}}}{T} + q\right)A,$$

where q – rate of cellular division.

The solution of the equation shows that the number of cells with aberrations A at any time t is equal to

$$A_t = \frac{k}{k\frac{D_{\text{макс}}}{T} + q} \cdot \frac{D_{\text{макс}}}{T}\left[1 - e^{-\left(k\frac{D_{\text{макс}}}{T} + q\right)t}\right],$$

and at the T twenty-four hour period, i.e., after the accumulation of dose $D_{\text{макс}}$,

$$A_T = \frac{kD_{\text{макс}}}{kD_{\text{макс}} + qT}\left(1 - e^{-kD_{\text{макс}} - qT}\right) = \frac{1}{1 + \frac{qT}{kD_{\text{макс}}}} \times$$

$$\times\left(1 - e^{-kD_{\text{макс}} - qT}\right) = \frac{1}{1 + 2{,}92qT}\left(1 - 0{,}776e^{-qT}\right);$$

$$A_0 = A_{T=0} = 1 - e^{-kD_{\text{макс}}};\ A_0 = 0{,}224;$$

$$e^{-kD_{\text{макс}}} = 1 - 0{,}224 = 0{,}776\ \frac{1}{kD_{\text{макс}}} = 3{,}92.$$

The values of A_T are taken from Table 36.

With the solution of the equation for T = 15-90 twenty-four hour periods, the average rate of cellular division constitutes

0.0435, which is an order higher than in the control animals as well as in rats following a single γ-irradiations at a dose of 150 rads. Consequently, the decrease in the number of aberrant cells with the reduction of the dose rate can be explained not only by the elimination of damaged cells, but also their reparation.[1]

Judging from the number of acentric fragments on the damaged cells, tentatively it is possible to assume that among the cells with aberrations, about 60% of them would have one damaged chromosome as well as about 40% – two and more (Table 37). If the restoration were to only encompass the cells with several damaged chromosomes, then it should not exceed 40%, which would be reflected in the relationship of the proportion of cells with a different number of damaged chromosomes.

Figure 34 presents the dependence of the number of cells of the liver with restored chromosomes on the duration of irradiation:

$$A = \frac{a-b}{a} \cdot 100\%,$$

where a – the expected number of cells at some period with chromosomal aberrations taking into account their possible elimination during division; b – observed number of cells with chromosomal damage during the same period (see Fig. 33).

The considered dependence for the same cumulative dose has a form of a curve, the upper branch of which trends toward 100%, and the lower one – towards 0. Consequently, it is possible to assume that the restoration has proceeded in the cells with two as well as with one damaged chromosomes. The absence of changes in the relationship of the properties of cells with one, two and more acentric fragments and pons for the different duration of irradiation is proof for drawing this conclusion. These data provide a basis to propose that in the majority of cells the restoration either

Table 37. Numb
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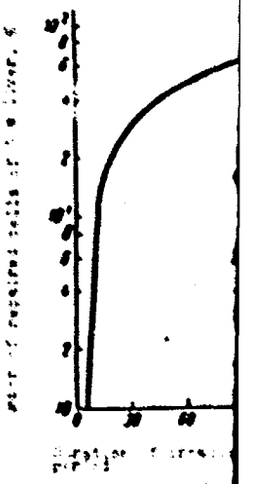
Duration of irradiation, twenty-four hour periods	One frag ment
Single	57,0±
15	68,0±
30	48,0±
45	56,0±
60	58,0
90	57,0±
180	68,0
Control (without irradiation)	80,0



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[1] I wish to express my gratitude to V. Yu. Urbakh for his aid in the mathematical treatment of the results.

Table 37. Number of cells of the liver of rats with individual forms of chromosomal aberrations following γ-irradiation of Co^{60} at a dose of 150 rads with respect to the total amount of cells with aberrations, %.

Duration of irradiation, twenty-four hour periods	One fragment	Two fragments	Three or more fragments	Pons and fragments	Pons	Number of fragments on damaged cells
ingle	57,0±3,5	17,0±2,3	11,0±2,4	11,0±1,8	4,0±2,0	1,3±0,05
15	68,0±3,5	15,0±2,3	6,0±1,6	5,0±1,5	6,0±1,0	1,2±0,04
30	48,0±6,7	19,0±3,0	13,0±5,9	12,0±4,6	8,0±1,8	1,4±0,10
45	56,0±3,4	16,0±2,4	8,0±1,7	14,0±2,6	6,0±1,3	1,3±0,06
60	58,0±3,3	20,0±2,4	8,0±2,4	7,0±1,5	7,0±1,4	1,3±0,04
90	67,0±3,7	12,0±2,3	6,0±1,8	14,0±1,6	11,0±2,5	1,1±0,06
180	68,0±2,3	16,0±3,1	7,0±1,6	9,0±2,1	0	1,3±0,004
control without irradiation	80,0±2,9	10,0±2,4	4,0±1,4	6,0±2,3	0	1,1±0,03

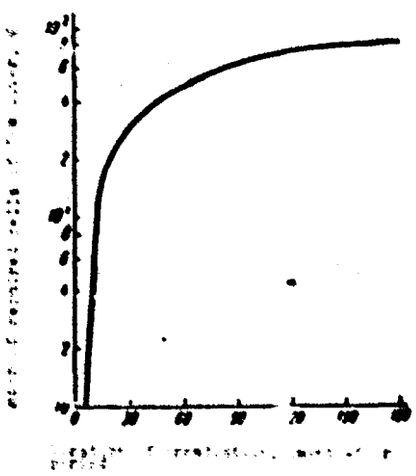

Fig. 34. Dependence of the number of cells of the liver with restored chromosomes on the duration of irradiation.

encompasses all of the damaged chromosomes, or did not take place in general. The last assumption requires a check of the material, making it possible to more accurately determine the number of damaged chromosomes in the cells. Considerations relative to the

possibility of such a "cellular" principle of restoration in plants was presented by N. V. Luchnikom [531, 532] and L. S. Tsarapkin [533].

The results of the described experiments agree with the data of Curtis and Crowlye [530, 534], who independent of us, but based on the same criterion, and in another form of the experiment (fractional irradiation of mice) observed the reduction of the effect of repeated X-ray irradiation in comparison with the effect of single exposure. During neutron irradiation the same authors did not detect any dependence on the dose rate [534]. Recently, a new communication appeared, about the possibility of reparation of chromosomal damage in quiescent cells of the liver of mice during prolonged irradiation [535]. The division of the cells of the livers caused by the injection of carbon tetrachloride, which by itself causes 30% aberration, in connection with how valid the author's work is regarded [535], should provide the preferance for hepatechtomy, applied in out experiments. Furthermore, the cited researchers neglected to record the mitotic activity and the elimination of cells associated with it. Possibly, this, in fact, was the reason for the certain reduction with time of the number of cells with aberrations even following single exposure [534].

The obtained data will not agree with the classical presentations [536] about the inevitable cumulation of damage of the chromosomal complex, existing as a result of a single-occurring event.

From the results of conducted investigation it is evident that with reduction of the dose rate, the mutated somatical effect is invariablely weakened just as observed for other clinical and physiological manifestations of radiation injury. G. P. Palyga [537], comprehensively studied the described phenomenon, compared the dependence of the appearance of chromosomal aberrations and changes in the peripheral blood on the dose rate. According to the data he obtained the clearest manifestations of the breakdown in the blood system were detected in rats, subjected to single exposure at a dose of 150 rads. According to the reduction in the dose rate, the changes in all indexes of white and red blood were

diminished, and at the least intensity of radiation exposure ($0.58 \cdot 10^{-3}$ rad/min) they were generally absent.

The absence of visible quantitative and qualitative changes in the peripheral blood is evidence of the fact that owing to the high plasticity of hemopoietic system during chronic exposure at such doses (approximately 0.8 rads per day) during a half of a year, the reparative processes prevail over the destructive processes. This condition is also known as compensation.

Thus, the overall dependence between the activity of physiological regeneration and the development of radiation changes and their normalization, shown by G. S. Strelin and coworkers is confirmed [472, 473, 475] using various specimens.

Consequently, in conclusion it can be said that the widespread opinion about the sharp differences between the so-called physiological consequences of irradiation and genetic damage, more accurately, karyological damage cannot be considered as valid. To say nothing of the indubitable interference of one on the other, leading to various functional disorders of an organism, the possibility of reparation is overall for them, and for some types of genetic damage the threshold effect as well.

Radioresistance and Antiradiation Protection of an Organism During an Early Postradiation Period

During the period between the overall irradiation of animals and the clinical recovery a phase change in the radioresistance of an organism [255, 539-547] takes place. Following the initial reduction in resistance to repeated irradiation through definite intervals (10-15 twenty-four hour periods for mice) the phase of increased radioresistance [539-541] advances, which is explained by various reasons [404], and specifically by the hyperregeneration of hemotherapy which is observed during these periods [255, 539, 541, 542].

The level of sensitivity to repeated irradiation does not coincide with the usual clinical criteria of illness [545, 548]. Obviously, the dynamics of radioresistance of an organism, most clearly determined by the method of repeated irradiations with a calculation of the lethal dose [$LD_{50/30}$] ($\Pi_{50/30}$) [255, 546-548], primarily is caused by the functional state of the limiting radiosensitive systems. Their restoration proceeds predominantly in accordance with the basic positions of Blair and Davidson [549] and is a head in the development of the various manifestations of a radiation syndrome.

Recently it was shown that the radio sensitivity of cells in a tissue culture undergoes changes even in the initial hours following irradiation. The tendency to analyze the reason for an S-shaped form of survival curves of cells of a mammal in vivo and in vitro served as a basis to conduct these experiments. As it is known, the curves of this type signify the least need of an accumulation of damage, preceding their lethal action [485]. If these damages are accumulated by a genetic apparatus, then the surviving cells should apparently contain recessive damage. The clarification by means of observing the survival of the progency of the surviving irradiation cells and as to whether this sublethal damage exhibits a hereditary pattern, served as a goal of the undertaken experiments. It turned out that over a certain time following irradiation (approximately corresponding to the duration of the delay of division induced by irradiation) the characteristics of survival of the surviving cells, and the irradiation of the cells become approximately the same as those in the original population. This provided a basis to conclude that the surviving cells are rapidly restored from damage and at the moment of the first cells division, the shown sublethal or recessive damage already is eliminated [484, 485].

In order to develop research on the antiradiation protection of animals during repeated irradiations, and especially with the introduction of protectors in the process of irradiation, it would be of interest to obtain information as to whether or not the restoration goes on in the cells in radio sensitive organs (primarily

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bone marrow and intestines) in vivo, which have received sublethal damage, whether or not it can appear in a radiosensitive organism and whether or not it will materialize more so by the reduction of radioresistance.

Results of corresponding experiments [372, 495, 496] serve as subjects of a subsequent account.

Based on the degree or radioresistance of mice during repeated irradiations the presence of postradiation restoration is judged, by determining the survival over 30 twenty-four hour periods following irradiation over the range of doses causing marrow death (700-800 rads) or the change in the duration of life at a dose of 1100 rads governing intestines death. As an additional means of estimating the studied phenomenon protectors are used with a known amount of dimishing dose factor [FUD] (ФУД).

Table 38 presents the results of experiments, in which the survival of animals is studied, which are subjected to double irradiation (300 + 420 rads) with an interval of 0; 1.5; 3; 6; 9; 12; 18 and 24 h, and prior to the second irradiation cystaphos is introduced (7 mg intraperitoneal injection).

Table 38. Survival of the mice during double irradiation at an cumulative dose of 720 rads (300 + 420 rads) under the effect of cystaphos, introduced before the second irradiation.

Interval between irradiation, h	Group	Number of mice	Survived		R	Average duration of life, twenty-four hour periods
			Number	%		
0	Control	30	1	3,3±3,5	—	8,8
	Experiment	30	13	43±9,0	<0,01	12,5
1,5	Control	30	6	20±73	—	13,9
	Experiment	30	15	50±9,1	<0,05	14,7
3	Control	30	11	37±8,8	—	13,5
	Experiment	30	17	57±9,0	<0,1	13,4
6	Control	30	13	43±9,0	—	15,1
	Experiment	30	22	73±8,1	<0,05	16,0
9	Control	30	16	53±8,9	—	14,6
	Experiment	30	26	87±6,1	<0,05	—
12	Control	30	3	10±4,1	—	10,0
	Experiment	30	24	80±7,2	<0,001	—
18	Control	30	11	37±8,8	—	13,0
	Experiment	30	24	80±7,2	<0,01	—
24	Control	50	20	40±6,9	—	11,8
	Experiment	50	43	86±4,7	<0,01	—

As can be seen from Fig. 35, in which the graphic analysis experimental data is presented, the interruption in irradiation at 1.5; 3; 6; 9; 18 and 24 h results in a reliable ($R < 0.01$) reduction of the damaging effect of the cumulative dose. If, over 18 and 24 h this can be explained by the beginning of regeneration, then in the earlier periods, specifically, over 3 and 6 h, when the mitotic activity of the bone marrow is almost completely suppressed, such explanation is unacceptable. Between them during these periods the survival increases by 20-50% in comparison with continuous irradiation. In the 9-12 h interval during irradiation radiosensitivity temporarily increases.

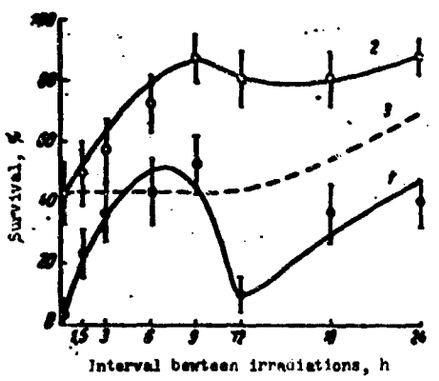

Fig. 35. Change in the survival of mice during double irradiation at a cumulative dose of 720 rads (300 rads + 420 rads). Reliable intervals during $R < 0.05$: ● – control; o– before the second irradiation, cystaphos is introduced; - - - the proposed level of protection without allowing for the restoration following the first irradiation.

The obtained data do agree with the mentioned experiments in the tissue culture and based on the analogy in explaining their hypothesis [484, 485] it can be interpreted as a result of the restoration of the viability of a part of the cells of the bone marrow, produced as a result of the first irradiation of sublethal damages. Because of this at the moment of repeated irradiation the background of unimpairedhemopoietic cells should increase. In order to check the given assumption the total number of karyocytes of the bone marrow in the femoral bone of a mouse is determined at the 3rd twenty-four hour period following irradiation, i.e., during the period of its greatest aplasia. Figure 36 presents the mean data, obtained during the analysis of the bone marrow of three groups of mice with 26 animals in each group. One of them (control) was

subjected to single exposure at a dose of 720 rads, and the two others (experimental) – to repeated exposure at doses of 300 and 420 rads at intervals of 3 or 12 h. As can be seen from Fig. 36, at a 3 hour interval, the number of karyocytes exceeds the level of the control animals by more than 30%, but at a 12 hour interruption it cannot be reliably distinguished from it.

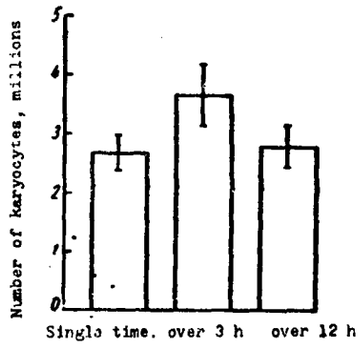

Fig. 36. Number of karyocytes in a femoral bone of a mouse at the 3rd twenty-four hour period following irradiation. Reliable intervals during $R \leq 0.01$.

Thus, the change in radioresistance of an organism, determined according to the resistance to repeated irradiation, actually can be associated with the state of the proliferational pool of the bone marrow. The active reparational processes begin in it immediately following irradiation and are carried out in the beginning as a result of the restoration of the viability of a part of the cellular population on the sublethal damage, and later as a result of regeneration.

The temporary increase in the radiosensitivity of an organism being observed in the interval between these processes can be governed by the first induced irradiation with the partial synchronization of the population of cells of the bone marrow, result of which the cells in the most radiosensitive generative stage succumb at the 10-12th h under irradiation.

Obtained results correlate with the data of the experiments, in which a possibility of postradiation restoration of cells of the bone marrow was shown in the research on their ability to form proliferating colonies in the spleen [486].

The results of experiments with cystaphos also are evidence of the presence of increased radioresistance of an organism in early postradiation period. If one considers that the amount of FUD, equal to 1.5 for cystaphos, over the range of doses of 300-700 rads does not substantially change (see Chapter IV), then during the first 9 h, the survival of animals, protected from the second dose, should not be substantially different from that observed at the zero interval of time (curve 3 in Fig. 35). However, as can be seen from Fig. 35, it increases in time, attaining at 6-9 h, 70-90%. Thus, with the allowance for FUD for the second dose, by this time no more than 40% injury induced by the initial irradiation remains.

In the following series of experiments the effect of breaking down the dose of 1100 rads by the average duration of life was studied; single exposure at this dose causes intestinal death of mice during 3-5 twenty-four hour periods. As can be seen from Table 39, during the application of radiation trauma using two or three methods at intervals of 1.5-24 h, the resistance of the animals to repeated irradiations likewise increases. This is noticeable during the analysis of the average duration of life (Fig. 37, curve 1), which increases to 6.2±0.31-9.3±0.4 twenty-four hour periods in comparison with 4.45±0.11 twenty-four hour periods during a single exposure, and is even more evident during the calculation of the number of animals, survived at the 4th twenty-four hour period following irradiation (see curve 2). During a single exposure more than 60% of the animals perishes at the 4th twenty-four hour period and only individual mice survive at the 6th twenty-four hour period. In all cases fractionating of the dose the reverse phenomenon is observed: at the 4th twenty-four hour period an insignificant number of mice perish (at a 24 hour interval by this time death is generally not observed, but the majority of animals live up to the 7-10th twenty-four hour periods and perish from injury of the organs due to hemopoiesis. Just as in the previous series of experiments,

Just as in the previous series of experiments, the lowering of the effect of the cumulative dose is governed by different causes: by regeneration at a twenty-four hour interval, and apparently, by the effect of restoration from damage to a part of cells of intestinal

Table 39. Average duration of life of mice depending on condition of irradiation.

Conditions of irradiation, doses, intervals	Number of mice	Average duration of life, twenty-four hour period	R
1100 rad, single time.	79	4.45±0.11	–
500 rads + 600 rads over 1.5 h.	69	6.2±0.31	<0.001
500 rads + 600 rads over 3 h.	60	7.5±0.16	<0.001
500 rads + 600 rads over 6 h.	59	6.9±0.23	<0.001
366 rads, 3 times over 1.5 h.	30	9.3±0.40	<0.001
500 rads + 600 rads over 24 h	20	8.2±0.45	<0.001

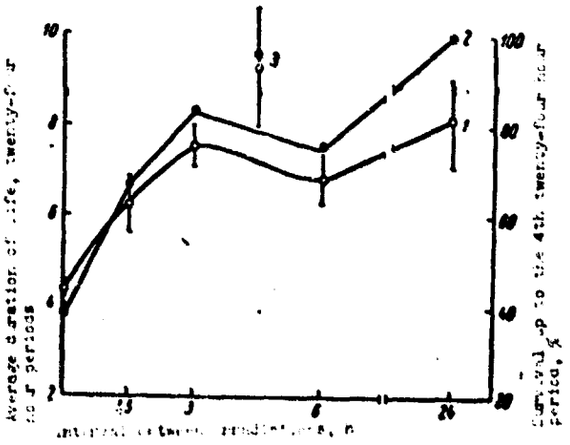

Fig. 37. Average duration of life (○) and survival of white mice up to the 4th twenty-four hour period (●) at single and repeated irradiation in a cumulative dose of 1100 rads. Reliable intervals during $R \leq 0.01$. 1 and 2 – 500 rads + 600 rads; 3 – 366 rads × 3 over 1.5 h.

epithelium during short interruptions between irradiations. Between prolonged periods a temporary increase in the radiosensitivity is noticeable. It proceeds even at the 6th hour interval, i.e., earlier than in the bone marrow, just as in the case of the whole dynamics of the process of change of radioresistance which takes place over shorter periods. This agrees with the conclusion about the crucial importance of the activity of reparation in lowering the effect of irradiation with a decrease in the dose rate, made during the morphological analysis of radiation injury in the crypt of the small intestines [458].

The same regularity was also revealed with mice of the C_3H line. From Fig. 38, in which the results of the experiment, carried out on 80 animals of a given line (40 mice per group) are presented, it is evident that the interruption in irradiation at the 3rd h governs the increase in the average duration of life from 3.65±0.07 twenty-four hour periods, which is observed during single exposure, up to 5.6±0.13 twenty-four hour periods ($R < 0.001$). The decrease in the average duration of life of mice of the C_3H line in comparison with the duration of life of white mice is explained by the high radiosensitivity of mice of C_3H line. In connection with this, only 5% of the animals survived at the 4th twenty-four hour period during single exposure at a dose of 1100 rads, whereas by breaking down this period, 95% of the mice survived (see Fig. 38a).

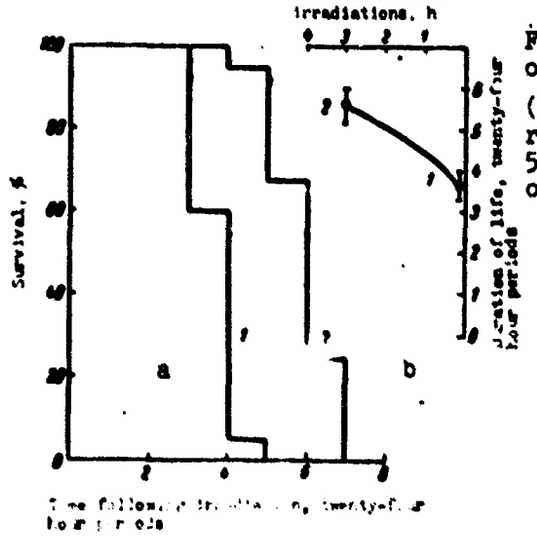

Fig. 38. Dynamics of death (a) of mice of C_3H line during single (1) irradiation at a dose of 1100 rads and double (2) at doses of 500 and 600 rads with an interval of 3 h.

An analysis of the results of experiments with protectors (Table 40) leads to a curious conclusion. During single exposure at a dose of 1100 rads, cystaphos facilitates the survival of only 15% of the mice; however, the duration of life is substantially increased, and the application of mexamine hardly affects the radioresistance. The obtained results become intelligible, if one considers that the FUD of both protectors constitutes 1.5, therefore, the dose is reduced approximately only to 700 rads, being absolutely lethal, since, as shown in Chapter V, cystaphos also shields the bone marrow, and intestines, but the protective effect of mexamine on the intestines is not generally covered. During the joint application of both protectors, FUD increases to 1.8 which also controls the survival of 35% of the animals in accordance with the remaining dose (approximately 600 rads).

During double irradiation at doses of 500 and 600 rads with an interval of 1.5 h, the separate application of protectors does not affect survival, but their combined introduction substantially intensifies the protective effect. The observed phenomenon can be explained by the fact that at a dose of 500 rads the portion of sublethal damage in the bone marrow is minute, and the selected time interval (1.5 h) is still insufficient for their maximum restoration. Therefore, despite the existing effect of restoration in the intestines, the increase in the duration of life provide evidence and the protected animals during individual application of protectors perish from the injury to the bone marrow as a result of the remaining highly effective cumulative dose (approximately 700 rads), but with combined protection a larger number of animals survives, than with single exposure, as a result of the portion of restorative effect in the intestines appearing because of the increase in the FUD.

The validity of such an explanation is partly confirmed in experiments with triple irradiation at doses of 366 rads. Here, the protective effect manifests itself even during individual application of the protectors. Notwithstanding, with the lengthening of the interval between irradiations, the degree of protection can increase because of large manifestation of restoration. As can

Table 40. Survival of mice, subjected to single or repeated irradiation at a cumulative dose of 1100 rads with the application of protectors before each irradiation.

Conditions of irradiation	Preparation, mg/mouse	Number of mice	Survived		Average duration of life, twenty-four hour period
			Number	%	
1100 rads, single	Physiological solution	79	0	0	4.45
	Cystaphos, 7	20	3	15	7.1
	Mexamine, 1, 5	19	0	0	5.3
	Cystaphos 7 + mexamine, 1, 5	20	7	35	8.7
500 rads + + 600 rads over 1.5 h	Physiological solution	69	0	0	6.2
	Cystaphos, 7	20	0	0	11.2
	Mexamine, 1, 5	20	0	0	7.2
	Cystaphos 7 + mexamine, 1, 5	20(2)*	9	50	11.5
366 rads × × 3 over 1.5 h	Physiological solution	30	0	0	9.3
	Cystaphos, 7	25	3	12	8.7
	Mexamine, 1, 5	20	2	10	10.8
	Mexamine, 0, 6	20	2	10	10.0
	Cystaphos, 5 + mexamine, 0, 6	20	4	20	11.4
	Cystaphos 7 + mexamine, 1, 5	60(14)*	26	57	12.8
500 rads + + 600 rads over 24 h	Physiological solution	20	0	0	8.2
	Cystaphos, 7	20	7	35	13.8
	Mexamine, 1, 5	20	5	25	10.6
	Cystaphos, 7 + mexamine, 1, 5	40	27	67	16.0

*In parentheses – number of mice, having succumbed in the first twenty-four hour period following irradiation.

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be seen from Table 40, at a 24-hour interval, the protective effect clearly manifests itself both with the individual and combined application of protectors, and between these two, the lowering of the effectiveness of the cumulative dose is difficult to explain by only the regenerative processes, considering the considerable quantity of the dose of the initial irradiation.

Postradiation Restoration of an Aspect of Antiradiation Protection of an Organism

Until recently, the term "postradiation restoration" meant uniquely the various reparative processes in a irradiated organism, the source of which are the unimpaired cellular elements. In this case the view was taken that a category of absolutely irreversible cellular injury exists; which does not lend itself to restoration, and consequently, results inevitably to the death of the cells. However, as far back as 1920, G. A. Nadson expressed doubt on the assertion of fatalism of primary radiation damage to cells having made the assumption about the possibility of their reversibility under determined conditions [550].

Radiobiological investigations in the last 10 years doubtlessly proved the reality of restoration of cells from the various types of radiation damage at all levels of organization of vegetative and animal world. This problem is comprehensively treated in special monographs [477, 479].

At present one ought to distinguish between two types of postradiation restoration: restoration, going on as a result of the proliferation which has preserved unimpaired cellular elements (regeneration in the broad sense of the work), and "true" restoration of the viability of damaged cells.[1]

[1]One ought to recognize that in the majority of observations, which offer evidence of the weakening of the primary radiation effect, including our experiments, the phenomenon of "true" restoration has not been proven in the strict sense of the word. Perhaps, it is more correct to speak of the characteristics of manifestation of injury under new conditions or about the liquidation of categories of reversed damages. However, such a treatment also isn't indicative.

The first which is characterized by the basic means of post-radiation reparation of an organism, specifically the bone marrow, was the subject of examination of the previous chapters. In this chapter certain new experimental material was presented, which is evidence of the presence of true restoration of damaged cells. Differences of the compared forms of restoration do not provide a basis for their contrast. Moreover, postradiation reparation of an integral organism doubtlessly includes all varieties of true restoration. Ramification of the latter has a fundamental scientific value, and furthermore, is of practical importance in connection with the possibility of modifying the injury by the application of different means following irradiation.

Namely from these positions an attempt of an analysis of the obtained experimental data will also be undertaken.

Thus, the restoration of cells from lethal damage can be considered as an overall pattern [479, 506]. Therefore, exceptions to it are interesting to examine [479]. Some of them refer to the absence of restoration in the cells of the liver, based on the preservation of chromosomal damage following a single exposure [515-518].

As the experiments themselves have shown in chronic exposure and in those conducted independent of our research with fractionated exposure [530, 534, 535], in the cells of the liver there is also a weakening of the effect of damage to the chromosomes. In this case the degree progressively increases in proportion to the decrease in the dose rate. On the basis of the cytological analysis in the distribution of the number of fragments on the damaged cells the assumption can be made about the fact that the restoration

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Therefore, the described phenomena can be valid and even expedient up to the corresponding experimental accuracy of the given problem, considering the result of "true" restoration, at least in contrast with the usual regeneration.

proceeds cell by cell [531-533] both in cells with two as well with one damaged chromosomes.

The obtained data require interpretations, which are distinguished from classical points of view according to which the so-called single-action events unavoidably accumulate [536]. Notwithstanding, the validity of the shown views [536] is limited by the phages and viruses and can extend to the cells of mammals. Probably, the appearance of chromosomal damage is not a single-action event; it has a certain potential metastable stage; possibly, in accordance with the "matrix hypothesis" of N. V. Luchnik, the chromosomal damage appears only as a result of the reduplication of dioxyoribonucleic acid [DNK] (ДНК) on the damaged matrix, which itself up to this moment can restore the original structure [488-490].

All these assumptions until now bear a rather speculative character and cannot be accepted without the corresponding experimental proof.

In principle, the important fact is that at a dose rate of 0.8 R/day, the number of cells with chromosomal aberrations did not exceed that observed in the nonirradiated animals at the same growth.

Consequently, it is necessary to admit that at such a level of radiation exposure either a complete restoration of chromosomes takes place, as a consequence of which the rate of mutation (according to form of mutations - chromosomal reconstruction) is not distinguishable from the spontaneous, or (as a final result, this is equivalent) the appearance of a chromosomal rupture is the same threshold reaction as in numerous other physiological manifestations of radiation injury.

Obtained data cannot include the effect of ionizing radiation in the calculation with a hygienic estimate; the effect until now has been built on the principles being threshold-free of the genetic effects of radiation. One can reason that the results of our investigations cannot completely extend into the fields of genetic

mutations, for which the threshold of the effect remains debatable, although the effect of restoration was also disclosed [492].

The data on the somatical effects of radiation agree with the data on the absence of some sort of noticeable deviations in millions of people, living for many generations in regions, where natural radioactivity somewhat exceeds the "average" level [551].

In any case, further accumulation of data on the effect of the low intensity of irradiation on the genetic apparatus of a cell is extremely interesting and important for a practical estimate of the danger of radioactivity in perspective, the revision of which is projected in a number of investigations [551-554].

The need for a differentiated approach to the classification of early and remote consequences of irradiation taking into account, the dose, the dose rate and type of exposure has been thoroughly reasoned out even at the level of the integral organism of G. D. Baysogolov and A. K. Gus'kov [555] on the basis of his observations and a critical examination of the literary data.

It was shown that the radioresistance of an organism increases in the first hours following irradiation. In contrast to subsequent regeneration this increase is controlled by the restoration of a part of the irradiated cells of the bone marrow or intestines due to sublethal damage.

Independent of us, an analogous conclusion on the partial restoration of an organism during the early postradiation period was also drawn by other researchers, who limited their observations to only an analysis of survival [556-558].

As experiments using protectors prior to a repeated dose of irradiation have shown, their effectiveness is determined by the amount of FUD and by the preferential protection of one or another radiosensitive system taking into account the level of radioresistance of the organism. In connection with this, during the early

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postradiation period (1.5-9 h following irradiation) the degree of protection not only has not diminished, as this could be expected on the basis of the results of works on the effect of irradiation to the effectiveness of protectors [177, 238, 239, 341], but has substantially increased, possibly, because of the partial restoration of the bone marrow and intestines due to sublethal damage, which appeared as a result of the initial irradiation.

At present it is not possible to accurately evaluate the nature of the appearing sublethal damage [485, 486, 559]. Most likely they exist as a consequence of injury of many structures of both nucleic and cytoplasmic origins and also include the retarding of cellular division, into a series of cumulative effects of irradiation [536].

The last data, obtained with the application of sophisticated histochemical methods of investigation [560] and phase contrast discontinuous filming using electron microscopy [561], is convincing evidence of the early damage of cytoplasmic structures (mitochondrias, Golgi's apparatus, various membranes). These changes even appear immediately following irradiation at relatively small doses (300-600 rads), and based on the thoroughly discussed conclusion [561] namely that they, not the genetic apparatus, are responsible for certain radiation injuries of the cells, specifically, for breakdown of the mitotic cycle.

The attempt of a universal interpretation of the dependence of a dose – effect for any cellular radiobiological reactions, undertaken by Hug and Kellerer [563] is interesting. They assumed that the logarithmic dependence between the dose and the magnitude of the effect, being the basic reason of the assumptions explaining the statistical pattern of the radiobiological effects by the heterogeneous distribution of the absorbed dose per unit of irradiated population or on the cellular "targets", can provide another interpretation. Hug and Kellerer consider the radiation damage of the cells as being dispersed whereby the observed unit reaction is manifested when the amount of damage exceeds that inherent to the given index

liability of the cells. For this fundamental quantity there esists an angle of the slope curve for the dose - the effect, plotted by semilogarithmic coordinates. This angle of the slope characterizes the "genetic activity" of the cells based on the studied criterion. With large doses the genetic activity attains maximum values which means the exhaustion of the compensating capabilities of the living system . The authors saw the confirmation of the validity of such an interpretation of dosage dependences in the results of experiments on the modification of radiation damage of cells using various exposures before and after irradiation. Despite the formal-mathematical pattern of the given reasonings [563], their appeal consists of the well-founded revision of orthodox assertions about the independence of radiation breakdowns of the genome and their leading value for any cellular reactions.

Convincing evidence of the independence of interphasal death on radiation injury of chromosomes was worked out by Yu. V. Korogodin [562].

Returning to the estimate of the phenomenon we observed, it is possible to propose, for example, that most of the radioresistance part of the population is restored from the damage, specifically, the cells, which are in the least perceptible stage of the cycle at the time of irradiation; consequently, the damage appeared to be even sublethal, in this sense, subliminal.

Nothwithstanding, these cells begin primary postradiation division, the reduction in the time of delay which can then be explained by the increase in the numbers of rehabilitated cells with the decrease in the dose. Then, in accordance with the data given in Chapter III about the kinetics of injury in bone marrow and the significance in the mechanism of protection of lowering the time of the mitotic blocking effect of hypoxia and of other protective factors, reminds the restoration from the sublethal damage is partly suggested.

The data from N. V. Luchnik and L. S Tsarapkin about the reparational rate and the decrease in the number of pathological

mitoses in pea seeds when wetting them in 0.01 *M* solution of cysteine for 48 h following irradiation [296, 488] will agree with this. The complete restoration of mitotic activity was also observed when moistening dry seeds of Vicia faba with a cysteine solution following their irradiation at a dose of 3,000 R [564]. The protective effect of cysteamine after irradiation was also detected in bacteria [565]. Notwithstanding, the therapeutic effect of cysteamine [328-332] and serotonin [326], for which thus far there is no satisfactory explanation, have an analogous nature. There is every reason to conduct special investigations for an estimate from these positions of adaptability of a protective means following irradiation at light and moderate doses, when the reduction in time of the mitotic block can exhibit a substantial effect, since at these doses the number of cells with aberrations of chromosomes will be relatively small. Whitefield Rickson [566] showed a considerable reduction (all the way to an absence) of postradiation delay in the division of cultures of cells in mice, upon the introduction of agmatine (decarboxylized arginine). Among the earlier ones it was shown that this compound exhibits an expressed protective effect on mice [567].

With neutron irradiation in contrast with X-ray radiation differences in radioresistance of mice with single or repeated irradiation at an interval of 4-6 h [556] are not observed, i.e., restoration from sublethal damage is absent. In this case, as the experiment itself has shown, the data of other researchers [145, 568], with neutron irradiation of "marrow" death is noted in not more than 20-30% of the animals at doses less than the minimum of absolutely lethal; remaining animals perish over the course of 4-6 twenty-four hour periods as a result of the injury of the intestines. Consequently, the cells of the intestines are more sensitive to neutron irradiation than the hemopoietic cells. This becomes understandable, if one takes into account the overall pattern of the dependence of the rate of reparation on the degree of inherent given tissue of proliferational activity [472-475] and if one accepts the absence of restoration due to sublethal damage. Then, the intestines just as the tissue with the largest proliferational activity should incur more damage as a result of which the animals

do not live ahead of schedules, which reflect the injury of hemopoiesis, perishing from the intestinal syndrome. The absence of the reparation of chromosomal ruptures was already noted in cells of liver with prolonged neutron irradiation [534]. Here, the absence of the effect of a fractionating dose or of changes in its dosage for remote effects of irradiation (premature aging, reduction of a lifetime) with neutron irradiation in contrast with their substantial weakening with analogous changes under conditions of X-ray irradiation [568, 569], can be attributed to the data.

All of this testifies to the direct connection of the degree of radiation injury of the cells with the amount of linear energy loss [LPE] (ЛПЭ). At high values of LPE the cells is damaged irreversibly, in connection with the fact that the restoration of its viability is impossible. It is highly probable that a large relative biological effectiveness [OBE] (ОБЭ) of plutonium-ionizing radiation in a relationship of direct (as a result of the injury of active proliferating organs), and especially remote (because of the subsequent realization of injury in the remaining somatical tissues) effects is taken into account associated with this phenomenon.

Obviously, the irreversible component of radiation injury to a certain extent is determined, namely, by such irreparable forms of cellular breakdowns which is also manifested in the form of a sharp increase in OBE of neutrons and other plutonium-ionizing radiations when evaluating remote consequences of irradiation in comparison with its immediate effects.

Conclusion

New experimental evidences is presented of the possibility of modifying radiation cellular breakdowns and radioresistance of an organism on the whole by changing the dose rate or by its fractionation.

The possibility of reparation of chromosomal damage in quiescent cells of the liver, and likewise the resotoration of viability of irradiated cells of the bone marrow and intestines, obviously,

eliminating sublethal damage was established.

The application of protectors in the early period of increased radioresistance of an organism is accompanied by a large increase in survival in comparison with that expected on the basis of the amount of FUD; which can be explained by the partial restoration of the bone marrow or intestines from the initial irradiation.

The assumption was expresssed about the generality of the processes of postradiation restoration with one of leading elements of protection – in the time of delay of cellular division.

The possible significance of the proportion of the restorable part of the injury and its irreversible component in immediate and remote effects of irradiation, was controlled.

C H A P T E R VII

PROTECTION POSTRADIATION RESTORATION AND REMOTE CONSEQUENCES OF IRRADIATION

In comparison with the vast number of works devoted to the action of protectors on the immediate effects of irradiation, the literature on the protection for the remote consequences is limited by a small number of investigations, and their results are very discrepant.

The most spread opinion on the subject is that the remote radiation effects are weakened to a lesser degree than are the immediate effects [23, 191].

According to some researchers, cysteine, β-mercaptoethylamine [MEA] (МЭА) and cystamine [570-574], as well as paraaminopropiophenone [575] affect neither the reduction of the lifetimes of irradiated mice and rats, nor the occurence of neoformations. Moreover, Mewissen and Marshall noted that under the effect of MEA and cystamine the occurence of neoformations increases [572]. According to other authors, aminoethylisothiuronium [AET] (АЭТ) or mercaptoethylguanidine [MEG] (МЭГ) increases the average duration of life of mice and somewhat lowers its number of neoformations [576]. It was shown that the retardation of granulocytic leukemia and the complete preservation of the lymph of the thyroid of mice, irradiated at doses of 150-300 R, under the influence MEG [577], is significant. In other works the same researchers [578-580] noted that the protective effect of AET in relationship to the reduction of the overall life is doubtful, but in relationship to the blastogenic effect it is confirmed by

decrease in the occurrence leukemia and thymicolymph [578, 579]; however, there was no effect on the appearance of neoformations on the breasts, ovaries, lungs and wombs neither by AET itself, nor by its combination from subsequent transplantation of the bone marrow [579, 580]. A clear-cut protective effect in relationship to the appearance of leukemia was also detected by the lymph under the effect of glutation during the irradiation of mice of the CF_1 line at a dose of 400 and 700 R [581].

For research on the cataractogenic effect of irradiation along with works, in which protective effect of thiols compounds [579, 582-584] is noted, there are works, where the contradictory information is presented [576, 578-580]. More well-defined observations on the degree of epilation and graying of the hair, which had a noticeably weakening effect due to the protectors [107, 580, 585, 586], and also observations on the development of hephrosclerosis, not adding to the protection were made [579, 580].

If we sum up the given data, it is possible to draw the conclusion that thiols protectors, apparently, facilitate a decrease in the cases of the appearance of tumoral hemopoietic system and weaken the injury of the hair cover. The remaining remote effects either shield weakly, or they manifest themselves to the same degree. This conclusion can be considered especially convincing after generalizing the work of the Oak Ridge researchers, carried out on voluminous and reliable material [580].

The data about the effect on the remote consequences of hypoxia and protectors, acting on the hypoxia mechanism is even the more modest. It was noted that under the effect of hypoxia the duration of life increases [587-589], is nefroskleroz nephrosclerosis, the development of leukemia, cataracts and graying of hair are weakened [587, 588]. With triple irradiation of male mice under the protection of serotonin at a cumulative dose of 2430 R, at the 200th, 300th and 360th twenty-four hour period 60, 40 and 10% respectively of the animals, having recovered from the acute

syndrome survived [390]. Comparing these data with the present works [580, 581, 590], with regard to the reduction of the life span per unit of dose (4-6 weeks per 100 R), we see that in the case of the protection it is possible to expect a longer lasting life in the mice.

M. V. Svyatukhin with co-authors [591] showed a lowering of the incidence of radiation lymphoid leukemia under the influence of mexamine and propamine in black mice of the C_{57} and the absence of protection from myeloid leukemia in noninbred mice.

Thus, the sum total of all works, which almost exhaust the corresponding source material, consists of the fact that the protection from remote consequences is expressed to a considerably lesser degree than that from the immediate effects of irradiation.

This phenomenon can be associated to those initial changes, amounting to the basis of remote radiation pathology, have no vital importance in the pathogeny of the acute radiation syndrome [592-594].

Among such breakdowns the nonlethal hereditary changes in the somatical cells should play the substantial role. Having appeared in the cambium elements of activity proliferating tissues, they can indefinitely reproduce in the form defective offspring for a long time which is shown, specifically, in the fluorescence analysis of cells of the bone marrow and in the peripheral blood at widely spaced periods following irradiation [595, 596].

Such a disturbance should play an even larger role in the somatical tissues with low physiological regeneration, where they are preserved and can affect the functional activity, as shown in the example of posttraumatic regeneration of nerval or bone tissues [471, 474, 476, 597, 598].

In the opinion of many researchers, based upon the detailed analysis of voluminous experimental material, the shortening of the overall life span as a result irradiation can be considered as

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At the same time from hypotheses explaining the mechanism of aging, the mutation theory [602-604] has wide favor according to which aging occurrs as a consequence of the accumulation of somatical mutations with age.

Correspondingly, the premature aging of an organism being observed as a result irradiations, the shortening of the life span [600-603, 605, 606] the appearance of tumors and leukemia [577, 607-609], in the opinion of supporters of the mutation theory of aging, are the consequence of the accumulation of mutations, as evidenced by the data of special investigations on the karyotype by workers of atomic projects [610-612].

There is every reason to agree with valid criticism of the mutation theory as being unique, in explaining the essence of remote consequences [613-615]; however, it is impossible to reject, in principle, the cellular basis of the etiology of the late somatical radiation effects [616] and, specifically, the role of recessive mutations and structural damage of the chromosomal complex in the vital activity of the tissues and the organism, keeping in mind the uninterrupted functional unity of the genome with its various physiological manifestations of vital activity in the cells and in the organism.

In connection with this, the question arises, as to how the protectors affect radiation damage of the cells of widely spaced tissues and its chromosomal complex.

For the resolution of this problem G. F. Palyga and O. P. Ol'shevskiy together with us undertook an investigation, having as a goal to explain the possibility of modifying the damage of nucleic structures in cells of the liver with the help of protectors.

The cells of the liver, possessing high metabolic activity, are characterized, as was indicated, by an extremely low mitotic index.

The surgical removal of 2/3rds of the liver stimulates a relatively synchronous preparation as well as the introduction of mitosis in a large number of the cells. In connection with this it is possible to investigate the effectiveness of protectors on the different phases of the cellular cycle.

The Effect of Protectors on the Appearance of Radiation Rehabilitation of Chromosomes in Cells of the Liver at Different Stages Interkinesis

In the preliminary experiments [25] the rats were subjected to overall γ-irradiation of Co^{60} at doses of 150, 300 and 600 rads. The experimental animals were injected with AET before irradiation, and the control – with physiological solution. Twenty-four hours following irradiation they exhibited partial hepatectomy, and even over 30 h – an anaphasal analysis of the number of aberrant cells in the regenerating portion according to the methods described in Chapter VI. Thus, it was possible to obtain a presentation about the effect of AET on the appearance of chromosomal rehabilitation during the irradiation of cells at the G_0, G_1 and S.

As can be seen from Table 41, differences between the experimental animal and controls, subjected to irradiation at the same dose, but without protectors, are insignificant and statistically unreliable. These results were rather unexpected, especially since, as was shown in experiments on mice (see Chapter IV), the concentration of AET in cells of the liver is the highest. Consequently, one of the penetrations of AET seems insufficient for the protection of the given tissue, specifically for preventing ruptures of the chromosomes in cells, predominantly occurring during the irradiations at the G_0 stage.

To investigate the effects of protectors on the radiation damage of chromosomes during other stages of interkinesis, the irradiation is carried out for 24 h, over 6 or 18 h following hepatectomy, when in accordance with the duration of stages [617, 618] the cells were located in the G_0, G_1 and S stages.

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Table 41. Number of cells of the liver with chromosomal aberrations, induced at the G_0 and G_1 stages, %.

Group	Dose, rads		
	150	300	600
AET + irradiation.	20.2±0.8	29.7±0.8	75.5±2.0
Physiological solution + irradiation.	22.6±1.1	36.5±2.8	77.8±1.8

Considering the radiation retardation of cellular division of the thyroid of animals of the fixation of material they were conducted over 22, 26, 30, 34, 39 and 44 h following the operation, which was always run in the morning hours except for the effects of the twenty-four hour rhytmics. AET, as well as mexamine were used as protectors. Irradiation was carried out at a dose of 300 rads.

As can be seeen from Fig. 39, in which the results of the generalized statistical analysis of the given experiments are presented, as well as from Table 42, AET does not substantially diminish radiation injury of chromosomes (based on the criterion of aberrations) nor at any of the stages of interkinesis. The protective effect of mexamine appeared distinct and was most clearly expressed at the S stage which agrees with the data about the preferential protection of this stage by serotonin and AET during the irradiation of the cells of man in a tissue culture at a dose of 50 and 100 R [293].

From Fig. 39 it also follows that based on the appearance of chromosomal rehabilitation, the radiosensitivity of the G_0, G_1 and S stages cannot be distinguished.

In the majority of works, devoted to the radiation effects on individual stages of the cellular cycle, the delay of the synthesis of dioxyribonucleic acid [DNK] (ДНК) and mitoses served as the criterion of injury induced by irradiation. All the authors agree in that the most effective irradiation for the suppression of the

Table 42. Coefficient of protection from chromosomal aberrations, induced by irradiation in cells of the livers, occurring at different stages of interkinesis.

Stage of interkinesis	Mexamine	AET
G_0	+0.48	+0.086
G_1	+0.31	-0.06
S	+0.63	+0.102

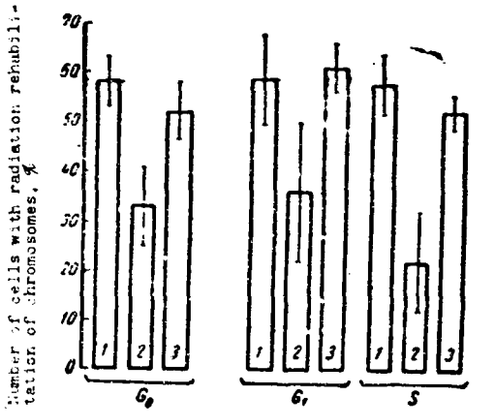

Fig. 39. The effect of protectors on the radiation rehabilitation of chromosomes in the cells of livers occurring at different stages of interkinesis. Reliable intervals during $R \leq 0.01$: 1 – control; 2 – mexamine; 3 – AET.

of the synthesis is at the G_1 stage [219, 618-620 and others]. Relative to the radiosensitivity of the different stages based on the degree of delay in mitoses, the data are ambiguous. Some have noted the greatest sensitivity of the cells at the G_1 and G_2 stage [618], others [268, 621, 622] – at the G_2 stage, the thi 1 [213, 623] – at the S and G_1 stage. The works, where the chromosomal aberrations served as an estimate of the damage of nucleus, it is less. Humphrey and others [621] showed that the exposure during the G_2 stage of the cells of the tissue culture from a chinese hamster has the greatest effect, whereas the cells at the G_1 and S stage based on radiosensitivity cannot be distinguished. Based on other data [624], the S stage of the cells from an ascitic crayfish are just as sensitive (if not more) to irradiation, as during G_2 stage. Our investigations provide evidence of the equal sensitivity

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G_0, G_1 and S stages to irradiation which agree with the mentioned present works [621], and likewise with the observations of G. P. Gruzdev about the equal radiosensitivity based on the criterion of all stages of the cellular cycle of the bone marrow of rats [300, 625].

Independent of our communications [25, 626] data have been published about the expressed protective effect of MEA in relationship to chromosomal aberrations of the cells of the liver of mice at the S stage [627, 628], which was observed only when performing the hepatectomy in the first 10 days following irradiation and it was absent at the 14th twenty-four hour period. In the shown investigations, the stimulation of the livers towards division was carried out with the help of carbon tetrachloride, which itself possesses a mutational effect, causing 34% chromosomal aberrations in the liver of mice [535]. Between those authors of the research [627, 628], despite the combined action of carbon tetrachloride and irradiations at a dose of 300 R they observed only 29.7% of the cells with aberrations in the control, and 22.1% in the protected animals. The shown circumstances complicate the interpretation of the obtained results and their comparison with our data.

Protection from Chromosomal Damage at Small Doses of Irradiation

On the strength of the assumption about the fact that with lowering of the radiation dose, the relative role of damage of genetic apparatus of the cell in comparison with the remaining consequences increases, it is of interest to study the possibility of protecting the hereditary structures.

It was shown that mexamine distinctly reduced the number of cells of the bone marrow of monkeys with chromosomal aberrations at a dose of 100 R [629, 630], in mice at a dose of 50 [268, 272] and 100 R [630]. Analogical results were obtained in experiments using a series of protectors during the irradiation at the same doses on tissues culture of man or of embryonic cells of a monkey [221, 293, 631-633]. However, during the exposure on the same

specimens γ-quantum at a dose of 25 R or X-rays at a dose of 12.5 R an abrupt drop or absence of the protective effect [293, 631-633] was noted. Considering the difficulty of the analysis of results in experiments on asynchronized tissues, in general, and at small doses, in particular, it is expedient to verify the same pattern on the quiescent cells of the liver.

For this purpose the rats were subjected to a daily irradiation at doses of 30, 25 or 10 rads up to the cumulative dose of 300 rads, since the experimental animal prior to each irradiation is injected intraperitoneally with cystaphos or mexamine. The obtained results compared with the data of corresponding experiments with single exposure irradiation at a dose of 300 rads.

As can be seen from Table 43, which reflects the results of three series of experiments, mexamine sharply reduced the number of cells with chromosomal aberrations at both a single exposure at a dose of 300 rads, and at single doses of 10, 25 and 30 rads; in all cases the coefficient of protection was equal to: 0.5-0.6. Cystaphos was less effective than mexamine, but more effective than AET in the previous experiments (see Table 43).

The obtained results uniquely give evidence about the fact that the protection by mexamine on the hereditary apparatus from chromosomal rehabilitation at doses of 10-30 rads is expressed to the same degree as at large doses.

The results of the given experiments support, in addition, the earlier drawn conclusions about the independence of the degree of protection from previous radiation exposure, because the amount of the coefficient of protection did not change, despite the 10-30 fold fractionating of the dose.

An analysis of the protection at lower radiation doses is associated with considerable difficulties, because in this case, the number of cells with aberrations only insignificantly exceeds the background. Under these conditions the obtaining of stati... lly

Table 43. ... during the ...

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Table 43. Effectiveness of the protection of cells of the liver during the G_0 of different radiation doses.

Conditions of irradiation	Number of cells with induced irradiation by chromosomal aberrations, %			Coefficient of protection	
	Physiological solution	Cystaphos	Mexamine	Cystaphos	Mexamine
300 rads, single exposure.	50±5.8	37.4±2.2	25.6±2.1	0.24±0.02	0.48±0.06
30 rads × 10 daily.	21.2±3.2	16.0±1.1	8.1±1.8	0.24±0.15	0.62±0.18
300 rads, single exposure.	50.3±2.7	–	20.9±2.8	–	0.58±0.18
25 rads × 12 daily.	28.2±3.4	–	13.2±2.8	–	0.53±0.13
300 rads, single exposure.	47.1±3.1	–	25.4±3.0	–	0.46±0.07
10 rads × 30 daily.	24.6±2.5	–	10.7±2.1	–	0.57±0.09
30 rads × 10 at intervals of 2-3 s.	48.7±2.7	–	–	–	–
10 rads × 30 at intervals of 2-3 s.	47.3±5.3	–	–	–	–

reliable differences in the absolute amount of protective effect requires a very large amount of experimental material.

The existence of a threshold of protection according to the criterion seems improbable to us. In any case one ought to give preference to the experimental analysis on the model of quiescent cells selected by us, which accumulate chromosomal damage rather, than actively dividing the cells.

In the conducted experiments one interesting experimental fact was disclosed – a significant decrease in the number of cells with chromosomal aberrations with the fractionating of the dose at a twenty-four hour interval.

Consequently, the weakening of radiation damage of chromosomes can proceed not only as a result of the lowering of the radiation dose rate (see Chapter VI), but also with its fractionating. The obtained data permits one to assert that this process requires a certain time, since during the splitting of the dose at intervals of 2-3 s, the number of cells with rehabilitation reconstruction is not distinguished from the number of cells, which appear during a single exposure at the same dose. As it was explained, restoration is completed at least in the course of a twenty-four hour period, since a further increase in the intervals between the fractions does not have an effect on the final action and the remaining damage of the chromosomes subsequently is preserved. This can also be explained by the absence of differences in the number of cells of the liver with aberrations at single and repeated irradiations, when the interval between them exceeds one twenty-four hour period [515-518].

Since the amount of a single dose (10-30 rads), also has no effect on the restoration research was undertaken by us on this process using a further decrease in the single dose up to 10, 7, 3, 5 and 0.7 rads at 10-, 20- and 100-multiple irradiations up to a cumulative dose of 100 and 70 rads. The selected single doses coincided approximately with twenty-four hour periodic doses during chronic irradiation in experiments, described in Chapter VI (5-10, 3.5 and 0.83 rads, respectively). As the analysis of the obtained results [634] showed, during fractionated irradiation over the range of doses of 0.7-10 rads the portion of restoring cells does not change and also cannot be distinguished from that observed at doses of 25-30 rads. During chronic irradiation (see Table 35), it was reduced with an increase in the dose rate, attaining 38% at a dose rate of 3.5×10^{-3} rad/min (10 rad/twenty-four hour period), i.e., up to an amount corresponding to the portion of the restoring cells during a fractionated irradiation over the range of doses of 0.7-30 rads. The dose rate following a definite value does not have an effect on the restoration of chromosomes, despite a difference of four orders.

The possibility of increasing the effect of restoration with a further decrease in the single dose (< 0.7 rad) during fractionated irradiation will be subject to a subsequent study, and as well as the minimum time, during which this process is completed.

Certain Characteristics of the Forming Irreversible Component in Radiosensitive and Radioresistant Organs when using Protectors

Comparing the results of described experiments with corresponding material, used in Chapter III, can lead to two conclusions.

1. The rate of the appearance of chromosomal rehabilitation under the effect of equivalent radiation doses in the bone marrow of mice and liver of rats is approximately equal (15-20% of the cells with rehabilitation for each 100 R). Consequently, according to the criterion of radiosensitivity of the bone marrow and liver there is very little difference.

2. The protective effect of thiols protectors is considerably more expressed in the cells of the bone marrow than in the liver. The effect of mexamine is approximately equal.

One ought to note that the effectiveness of chemical protection depends on different causes, sometimes inexplicable at the current level of knowledge. For example, cystamine, by substantially lowering radiation injury of thymocytes in vitro, does not affect the same cells in vivo [146, 149]. The protection for fibroblasts of a mouse in a tissue culture was not detected in the case of using cystamine and MEA, whereas AET was highly effective [153].

Furthermore, the lack of the protective effect in thiols protectors in relationship to the induction of chromosmal rehabilitation in no way means that they are not able to affect a number of other disturbances. It was shown, specifically, that in cells of the

same liver, cystamine facilitates the activation of mitoses [611], shields the synthesis of DNK [234, 281], and MEA weakens the disturbances of the glycogen-forming function [635, 636], already appearing soon following irradiation [637, 639].

Nevertheless there is reason to believe that in other tissues and organs as well, which are characterized by low physiological proliferational activity, the greater portion of the cells exising in the interkinetic state [25] remain unprotected from damage of the chromosomal complex, but this facilitates the accumulation of somatical mutations in the organism and the development of corresponding remote consequences. More recently this assumption was also expressed by other authors [640]. The point of view held by S. N. Aleksandr and K. F. Galkovskaya [338] is approximate and is, based on the presentations of two categories of pathological changes under the effect of irradiation, establishing that the protectors do not affect some of them (determinable recovery).

In contrast to thiols protectors the amount of protective effect of mexamine on the criterion of chromosmal rehabilitation in the liver, as mentioned, was of the same order as that in radiosensitive organs; for example, in the bone marrow. The FUD in both cases is approximately equal to 2.

However, for the development of remote radiation pathology is the same amount of FUD in the actively-or weakly regenerating tissues equivalent?

Obviously, it isn't. In actively proliferating organs, cells, supporting lethal chromosome rearrangements, perish during the first mitoses, and are eliminated from the population. It is possible to admit that only a certain portion of the cambium cells maintains recessive damage and exists as the supplier of defective offspring. Furthermore, the greater part of the cells of many radiosensitive organs perishes during the interphase, and likewise is replaced by new, unimpaired cells. In non-dividing and differentiated tissues of such a form, death, as already mentioned

in the example of livers [360], is not observed.

Consequently, in the majority of differentiated somatical tissues, even in the case of partial protection, an incomparably large number of cells with a pathological chromosomal complex is retained.

Here, it is appropriate to recall that the protection from remote consequences is most clearly shown in the relation of certain leukemia with lymph, epilation and graying of hair, i.e., in addition to actively proliferating tissues. Less clear protection from the appearance of other tumors and premature aging, according to the mutation theory, can be associated with the nonprotected and irreversible component of injury in the majority of somatical tissues of an organism.

At present information for the causes of differentiated protection of cells of an organism by selected protectors is lacking. It is only possible to assume that mexamine causing general hypoxia, creates conditions for the manifestation of an oxygen effect whose symptons are commonly known. As for the thiols protectors, here the biochemical features of cells with different proliferational activity with a degree of differentiation can play the role.

In dealing with the preservation of the many somatical mutations, one ought to also have in mind another series of serious disturbances in an irradiated organism, also not being protected or only weakly protected by protectors. A part of them is also the result of mutation events, the others are even of an epigenetic nature. Such disturbances are related to remote immunological consequences of irradiation (lowering of the natural immunity and immunogenesis), the normalization of which proceeds only through wide intervals of time which also affect the state of the organism on the whole, including its lifespan [592-594, 641].

Based on the data about the introduction of bone marrow, irradiated in vitro in the presence of AET, 90-100% of the irradiated recipients survived without an increase in the number of secondary illnesses

(of an immunologic nature), the assumption was expressed about the preferential protection of hemopoietic cells in comparison with immunized competence [642-645]. Subsequently, this point of view found confirmation in the original experiments from successful transplantation of homologous cells of the liver of animals, preliminarily protected with AET or aminopropylmethylisothiuronium [APMT] (АПМТ) [Translator's Note: not definable in available sources] [646].

Ye. I. Lavrenchik [647] succeeded in demonstrating that AET, by substantially weakening certain autoallergic radiation reactions, does not affect the radiation change in the structure of the nucleoproteid fraction of the liver. The protective effect of cysteine in relationship to radiation injury in the immunogenesis in rabbits [648] could not be detected.

All this data [642-648], however, can be given another interpretation as well: possibly, the injury of the investigated systems already takes place at small doses, in connection with whether or not their the protection over the range of moderately lethal doses can be detected.

Other numerous functional breakdowns [404, 405, 594, 639, 649], the degree of protection of which adds difficult to the quantiative estimate in the composition of the irreversible component of radiation injury, to a certain extent, determine the remote consequences.

Notwithstanding, the lowering of the functional activity of hemopoiesis at a large cumulative dose or at widely spaced periods following irradiation, is partially governed by anomalies of the genome in cells of the regulating systems (nerval and endocrine) as is known, hardly dividing and retaining the chromosomal damage. Then, too, for the protected animals the shown disorders of hemopoiesis should be strongly expressed, because even in the case of the partial weakening of chromosomal disturbances, nevertheless, a vast number of cells of the regulating systems will contain defective genome in the functional relation.

Thus, along with two types of postradiation restoration, associated with the immediate effects of irradiation, there exists a third, generalizing type – the postradiation restoration with widely spaced periods integrating a whole variety of radiation injury. It is natural that the latter is complicated in proportion to a transition from a less organized to a more developed one in the evolutionary relation of biological items.

Successful research on remote pathology and ways of weakening it, consequently, depends again – on the degree of approach of our assumptions towards a correct understanding of the initial processes of radiation injury.

This conclusion is especially important, if one has in mind the difficulty of a quantitative estimate of the protection of the most remote consequences in connection with the various factors of the media, hardly reproducing under normal conditions of a vivarium, during a long experiment. This truth is insignificant in reference to the estimate of the overall lifespan and especially the research on the blastogenic effect because of the complex dose dependence of the "riddance" of tumors [608, 613].

Conclusion

The differentiated effect of thiols protectors (AET and cystaphos) as well as mexamine on the appearance of structural damage of the chromosomal complex in cells of the liver of rats, which exist at the time of irradiation at various stages of mitotic cycle, was established. Thiols protectors either weakly diminish or not at all the number of cells with chromosomal aberrations during the studied stages of interkinesis (G_0, G_1, S).

Mexamine substantially reduces the number of aberrant cells at all stages: the most expressed protective effect manifests itself during the stage of the synthesis of DNK (PNP : 2).

Protective effect of protectors according to the criterion

(chromosomal aberrations) is manifests itself to an equal degree over a considerable range of doses (25-300 rads) without which - there is also a tendency for a decrease during small doses of irradiation.

The results of the experiments are discussed in connection with the data about the weakening or absence of chemical protection of remote consequences of irradiation from the position of mutation theory.

The accumulation of somatical mutations to a certain degree constitutes an irreversible component of radiation injury of the organism, determining the disturbance of certain physiological functions in the process of postradiation restoration. In organs, which can distinguish the high rate of physiological regeneration (bone marrow, intestines and others), carry out in time the elimination of such defective cells with the replacement of unimpaired ones. Therefore, in these devices the irreversible component manifests itself predominantly as immediate effects of the irradiation and only because of the preserved cabium cellular elements with the damaged genome in remote consequences [650].

In organs with low physiological proliferational activity, the absolute majority of cells preserves the chromosomal damage, and this determines the preferential development of the remote consequences and hardly affects the immediate radiation reactions.

The investigated processes, obviously, can be substantially weakened by the protectors, since even in the case of the number of somatical mutations, there remains a rather large number of cells with preserved injury of the genome (including cells of the nerval and endocrine systems), serving as sources of the sought-for information and breakdown of the regulation of the cellular functions.

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C H A P T E R IX

PRACTICAL ASPECTS OF ANTI-RADIATION PROTECTION

Voluminous literary material and its never-ending experimentation in the field of experimental anti-radiation chemical protection impelled us to conduct an analysis of these data in 1962-1964 as an aspect of the practical utilization of protectors. As a result basic limitations were formulated, difficulties, connected with using the contemporary preparations for the purpose of protecting man [6, 7], were enumerated, and likewise certain perspectives of overcoming them were outlined [137, 712].

The Feasibility of Protectors for the Protection of Man

Despite considerable successes, achieved in the field of experimental prophylaxis of radiation injury, the possibility of using chemical means for the protection of man has been problematic until now.

On this account there exists two diametrical contradictory points of view.

A number of research workers consider the utilization of contemporary protectors by man as not very promising [14, 18, 713]. In the opinion of others, such a possibility does not cause reason to doubt [3, 12, 49]. According to the initial presentation of Bacq and Alexander, ".. better protection of the armed forces, personnel of civil defense and the population can be provided for by the action of an intensity less than that of ionizing [illegible] by the [illegible]

injection of 200-400 mg of cysteamine" [69]. However, more recently they have rejected such presumptuous statements [15, 714]. A. S. Mozzhukhin, F. Yu. Rachinskiy and L. I. Tarn indicate the possibility in principle of chemical prophylaxis for the purpose of protecting people, but they consider that the practical utilization of contemporary protectors up to now is impossible because of the side effects [9, 12].

In accordance with Doerti who considers that the comparative estimate of the protective compounds in reference to their feasibility for utilization by man has been indeterminate until now [181], and in our opinion, there are no sufficient grounds for the solution of the given problem.

Usually, they indicate three basic reasons complicating the practical utilization of protectors in general, including radiation therapeutics of tumors:

1) narrow therapeutic latitude;

2) ineffectiveness with fractionated irradiation;

3) the need for preferential protection of sound tissues without the weakening of the anticancerous effect of radiation.

Let us examine each of the listed reasons.

The optimum protective effect is observed when introducing large (close to toxic) numbers of protectors, which in experimental animals cause marked reactions of the nerval, cardio-vascular system, gastroenteritic tract, respiratory and others [9, 10, 12, 14, 35 and others]. When using lesser numbers of preparations, not causing the indicated side reactions, obviously, there is no direct relationship with the mechanism of protection [7], the protective effect is sharply reduced or is generally absent. According to the recommendation of the pharmacological committee, the doses of protector, intended for a man, should not cause side-line phenomena,

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and that is what causes doubt in the effectiveness of these doses in the radioprotective relationship.

The number of thiols protectors [MEA] (МЭА) ß-mercaptoethylamine, cystamine, [AET], (АЭТ) aminoethylisothiuronium, which man can transfer, is 20-25 times less effective than the doses transferable by mice (calculated per 1 kilogram of weight), and the corresponding concentrations of indolylalkylamines, according to [831], differ by 50-100 fold.[1]

Our attention was directed to the insolvency of the given arguments [137], since it is known that the doses of pharmacological active compounds for man, as is the rule, are notably different from doses transferable by animals. For example, the effective doses of morphine and adrenaline for man are 30 and 100 times less, respectively, than for mice. It was also known that there are considerable interspecies differences, depending on the method of entry. For example, in a mouse - rat - dog - monkey series the transferable doses of mexamine for mice introduced by parenteral means exceeded by 5-10 times the corresponding doses for monkeys, and especially, for rats and dogs. Among all those introduced inside the dogs, monkeys and mice, approximately equal amounts of preparation (more than 250 mg/kg) were transferred.

Furthermore, as the investigations indicated [392, 436], in addition to our experiments (see Chapter V), the effective doses of protectors were reduced during their combined application.

Thus, until now there are no grounds to assert, as well as to deny, the effectiveness of transferable amounts of protectors by man, especially those found as pharmacologically active compounds.

The limitations, associated with the lowering of the effectiveness of the protection with fractionated irradiation, following from the

[1] As is shown further on, these differences diminished to 5-10 fold.

material in Chapters IV and V, require a substantial correction, and that is why in the cases of overall repeated irradiation it is not discussed more here. As for the repeated local irradiation, characteristic for radiation therapeutics of tumors such data, generally, have not been received.

A very serious restraint is put on the means of utilizing protectors in the oncological clinic - the need of the preferential protection of normal tissues in comparison with tumors. According to Herve and Neucom [328], MEA weakens the radiation suppression of tumoral growth. At the same time the penetration of S^{35}-MEA in tumoral tissues proceeds less intensively, than in normal tissues [736], and cystamine generally does not seem to be effective during the irradiation of Walker carcinoma of rats [737].

These problems were studied in greater detail in relation to AET. Just as special radiometric investigations showed, this protector, tagged with S^{35}, actually penetrates solid and ascitic tumors in a considerably less amount in comparison with normal tissues, in which one can also associate its ineffectiveness during the irradiation of a number of transplanted tumors [181, 348, 738-745].

Only one work is known, in which the differences in the distribution of H^3-AET in normal and cancerous tissues of mice during histoautoradiographic investigation was not detected [746]. N. I. Shapiro and Ye. N. Tolkacheva noted that except for the selective distribution of protectors, which in itself can depend upon time and means of their utilization, an indubitable role should be played by the morphological and pathophysiological features of turmoral growth in general and by the specific character of the separate forms of tumors [290, 747, 748]. Specifically, inasmuch as the aeration of normal tissues is higher than in tumoral ones, then the effect of the protectors with a hypoxical mechanism of the action in normal cells will be greater than in tumors [748].

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Therefore, actual research on the new protectors remains, and likewise the pursuance of research on other experimental models, specifically on spontaneous tumors (in this case one ought to keep in mind that the described regularities were established only for the transplanted tumors).

About the Criteria of the Radioprotective Effect Possessed by Man

Recommendations about the feasibility of protectors to protect man basically rest on the results of their clinical tests which have nothing in common with conditions, under which the radioprotective effect in the experiment is observed.

On the strength of the presentations about the crucial importance of protectors to protect only a small part of hemopoietic tissue in the mechanism of effect, it is difficult to give meaning to the utilization of their regional radiation therapeutics, when from the radiation exposure the greater part of the productive hemopoietic tissue remains intact.

Moreover, thus far the nature of leukopenial conditions, which have developed as a result of prolonged local radiation load, is not clear. Quite probably, during their formation various neurohormonal factors, including those of toxic nature participate, in a relationship to which the effect of protectors was not studied. In contrast with the published data [1...], L. I. Kublik, in modeling an experiment on rats using conditions of radiation therapeutics, did not observe any substantial leucopenia (except for insignificant lymphopenia) with massive irradiation of a tumor on the femur (up to 10,000 R) and with thorough protection of the remaining parts of the body.

Notwithstanding, the observed transient lymphopenia with local irradiation is the consequence of the failure of the lymphocytes in the peripheral blood, moving with the blood circulation through the zone of irradiation. As evidence of this we also conducted a

retrospective analysis of the results of the investigation of the blood of a sick mammary cell, subjected to local irradiation in connection with cancer of the oseophagus, with which a rapid transient and absolute lymphopenia always developed following a cumulative dose of 1500-2000 rads.

According to the data from A. A. Klimenko, of 30 sick leucocytes, in which a decrease in their number of leucocytes below 3000 per 1 mm^3 was observed as a result of radiation therapeutics, the changes in the bone marrow were extremely insignificant [716].

In principle, the other reason for radiation reactions of organism at a massed site (exceeding doses by 70 times, which cause "X-ray hang-over" in people), the local [328] or general irradiation at moderately lethal doses during partial screening [322, 327] is evidenced in investigations, in which the effect of MEA was observed during its utilization not only in the irradiation of mice and rats, but following it, as well.

When evaluating the application of cystamine, MEA [69, 329-331, 717-725] and mexamine in the clinic [831] a weakening of a series of reactions from the irradiation (nausea, vomitings, feelings of disturbance, and etc.) was indicated. In this case the effect of the preparations manifested itself with its application not only prior to irradiation, but also following it [69, 329-331, 831]. One should note that protectors showed the weakest effect on the quantitative composition of the peripheral blood, but according to certain data, it was not generally exhibited [726, 727].

Notwithstanding, the described weakening of the primary radiation reaction was governed just as much by the radioprotective features of the protectors (more so when used following irradiation), as by other pharmacological effects, specifically by a neurotropic effect. Evidence of this are the results of the analysis of more than 1000 cases in the utilization of the various compounds (pyridoxine, derivatives of phenothiazine, tranquilizers and other means), on patients, undergoing X-ray therapy for malignant tumors. The

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radiation reaction was completely eliminated or substantially weakened [728] by 60-90%, although the shown compounds, if at all do not possess radioprotective features, or show a very weak protective effect. The improvement of the overall condition can, to a certain extent, even affect the indexes of the peripheral blood. This to an equal degree relates to other works, the data of which are evidence of the weakening of radiation reactions under the effect of preventive or therapeutic application of various means: prednisone [729], 1-diphenylmethyl 4-metylpiperazine [730], amino acids [731] and other means [732-735].

Thus, the existing material does not provide sufficient grounds either for confiming the feasibility of a radioprotective (in the true sense of the word) effect of protectors for man, or for excluding such a possibility.

Among them absolutely adequate objective criteria exist for an estimate of the effectiveness of protectors on man. As it follows from the material, presented in Chapters III-V, it is possible to recommend as such criterion a calculation of cells with chromosomal aberrations in a section of the bone marrow of man, subjected to the immediate local irradiation with the process of radiation therapeutics. The reducing in their number provides every reason to ascertain the presence of the protective effect, and likewise permits one to describe the quantitative degree of effect of any of the investigated protectors.

Furthermore, for indolylaklylamines or other preparations with a hypoxia mechanism of action it is possible to successfully employ a polarographic determination of the level of oxygen concentration in tissues, the reducing of which will permit one to confidently state the effectiveness of the tested dose in the preparation.

In reference to aminothiols information would be valuable for their utilization in the chemotherapy of tumors with radiometric compounds, which when conducted under clinical conditions, in principle, cannot be distinguished from the experiment on animals. In this case the overall action of the alkylating agent takes place, and in the

case of substantiation of the possibility of weakening the radiometrical intoxication with the help of protectors, the corresponding data could be extrapolated on rather firm grounds to a human even as it applies to radiation exposure.

The examination of causes complicating practical application of protectors, and likewise the material from their clinical tests, is assurance that this problem still is insufficiently studied for an alternative decision one way or the other.

In connection with this we have initiated corresponding experimental-clinical investigations first at the Moscow Oncological Institute named after P. A. Gertsen, and then at the Institute of Experimental and Clinical Oncology, AMN (Academy of Medical Sciences), USSR, results of which will be used in subsequent discussion.

Distribution of Cystaphos in an Organism of Animals with Primarily Innoculated and Spontaneous Tumors

G. M. Ayrapet'yan, L. Kh. Eydus and others [749, 750] together with us studied the distribution of cystaphos in an organism. This compound was thoroughly studied by Akerfeld [751, 752], who maintained specifically that under the effect of phosphomonoesterase fermentative hydrolysis of the S–P bond takes place with the liberation of MEA and orthophosphate. The shown investigations are conducted in experiments in vitro. There is no information on the chemical transformations of cystaphos in an organism and the characteristics of its distribution throughout the organs.

The assignment of the investigation consisted of the research on the dynamics of the spread of cystaphos in various organs and tumors of mammals taking into account the assumed breaking down of orthophosphate in the organism. For this purpose preparations of a protector, tagged either with S^{35}, or P^{32} were used. The specific activity amounted to 10-15 mCi/g for sulfur and 1-5 mCi/g for phosphorus.

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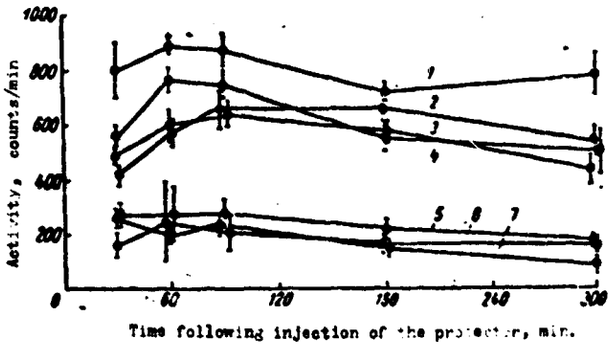
The distribution of cystaphos in the organism was studied in white noninbred mature rats, predominantly females, with transplanted M-1 sarcomas, on adult mice of the C_3H line (females) with spontaneous and transplanted adenocarcinoma of the milk gland and on noncancerous animals.

S^{35}-cystaphos was introduced at 20 mCi per mouse and 100 mCi per rat, and P^{32}-cystaphos at 0.5 and 5 mCi, respectively, independent of the weight of the animal. With the addition of the inactive compound to the radioactive preparation the total dose of cystaphos was brought up to 7 or 70 mg per animal, respectively. The preparation was dissolved in a physiological solution and injected under the skin of the back at a volume of 0.2 ml per mouse and 0.4 ml per rat. Homogenates of the tissues were prepared from the entire mass of the organs, and the homogenates of the tumors - separately from the peripheral and its central sections. The radioactivity of S^{35} was measured in the thick layer (more than 24 mg/cm^2), and P^{32} - in the thin layer.

The absolute number of protector existing in the tissue at one given instant or another, was determined by means of the comparison of radioactivity with the counting rate of standard samples, prepared from solutions introduced into the animal (all of the observed radioactivity was attributed to the effective form of the protector, and the possible biochemical transformations of cysteamine were not considered). In experiments with rats the counting rate of S^{35}, equal to 1000 counts/min, corresponded to a concentration of the protector in the tissue of 0.56 mg/g; in the experiments with mice - 0.28 mg/g.

As can be seen from Fig. 46, the results of the measurements of the radioactivity of S^{35} at different periods following the introduction of the preparation in the rats are presented, and the dynamics of the spreading cystaphos in the normal tissues of the investigated organs are approximately equal. The disseminated maximum concentration of the tagging was read between the first and second hours following introduction. The concentration of the tagging differed little in



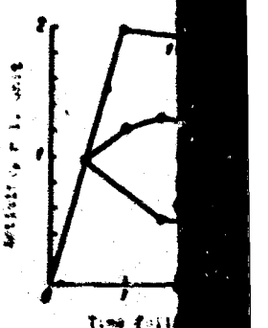
Time following injection of the preparation, min.

Fig. 46. Change in the radioactivity of the various organs of rats after the introduction of S^{35}-cystaphos: 1 - bone marrow; 2 - liver; 3 - spleen; 4 - intestines; 5 and 6 - tumor (peripheral and central sections, respectively); 7 - blood.

the individual organs and sharply (by 2.5-3 times) exceeded the corresponding values for tumoral tissue during the entire period of observation (5 h following introduction). Such a considerable difference, associated, apparently, with the characteristics of the blood supply of tumors, is encouraging as far as the relationship to the therapy of certain forms of tumors in man goes. The difference between the concentration of tagging in the central and peripheral sections of a tumor was caused, probably, by the same factor that one must also consider under definite conditions with therapeutics.

As can be seen from Fig. 47, the spread of S^{35}-cystaphos in the tissue of mice proceeds considerably faster than in the tissue of rats. This is exhibited by a more sharply expressed maximum, already spreading for a period of 30 min following injection, and is approximately doubled in the concentration of the marking during this time in comparison with rats (taking into account the differences in the induced activity). The difference in the dynamics of the spread of cystaphos in the tissue of mice and rats is reflected in Fig. 48.

The high rate of the dissemination of cystaphos in the tissue of mice correlates with their accelerated blood circulation in comparison with the blood circulation of rats. The apparent differences



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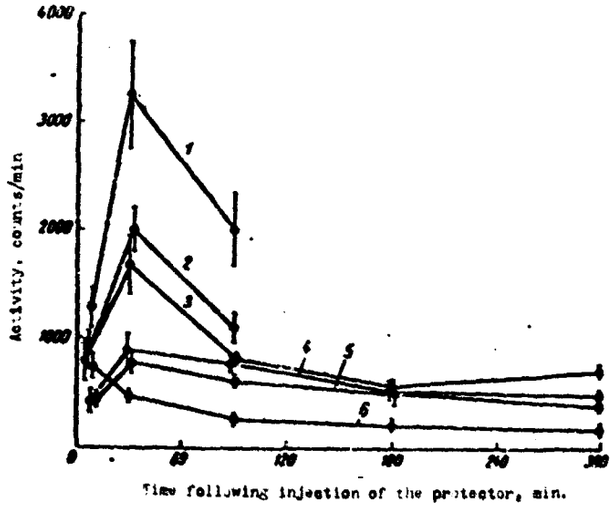

Fig. 47. Change in the radioactivity of various organs of mice following the introduction of S^{35}-cystaphos: 1 - liver; 2 - intestines; 3 - spleen; 4 and 5 - tumor (peripheral and central sections, respectively); 6 - blood.

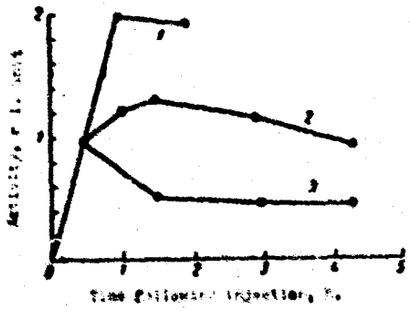

Fig. 48. Relative change in the radioactivity of normal tissues of animals after the introduction of P^{32} or P^{35}-cystaphos. Each point was made based on the averaging out of all investigated tissues (except for the blood and tumors) counting rate at a given moment to the count for 30 minutes following introduction, assuming unity of the latter: 1 - rats, P^{32}; 2 - rats S^{35}; 3 - mice, S^{35}.

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detectable h re are highly significant (for example, the position of the maximum with time differs by approximately 3 times), and one need not consider just the radiation therapeutics of the tumors, but also the research on the chemical protection from the effect of the radiation, as well. In this connection it appears to be invalid that in the majority of the experiments on anti-radiation chemical protection, the protectors are parenterally injected usually from 5-15 min

prior to irradiation independent of the species of animal, not considering the means of introduction and the duration of irradiation. Under such conditions the comparison of data on the effectiveness of the protection by the protectors and the optimization of the protection presented by various authors, is very difficult to make. If, based on our data and it is assumed that the presence of radioactive sulfur characterizes the active state of the protector, then with intensive irradiation the optimum for the protection of mice using subcutaneous injection would be a period of 30 min of irradiation, and in rats, 60-90 min.

Presented in Table 56 are the results of direct experiments, conducted for the purpose of determining the optimum on the effectiveness of protection for the period of introduction of cystaphos prior to irradiation of mice and rats at doses of 720 and 900 rads, respectively. Taking into account the duration of irradiation, the maxima of the curves of effectiveness of protection correspond to the maximum of concentration of the protector in the tissues of animals (Fig. 49).

Table 56. Dependence of survival in animals on the time of a subcutaneous injection of cystaphos (350 mg/kg).

Interval between injection and irradiation, min.	Mouse, 720 rads			Rats, 900 rads		
	No.	Survived at the 30th 24 hour period		No.	Survived at the 30th 24 hour period	
		No.	%		No.	%
Control	50	0	-	40	0	-
-20	80	53	-	60	38	63 ± 6.3
40	50	32	66 ± 5.3	30	19	63 ± 8.9
60	70	33	44 ± 7.1	34	28	82 ± 6.6
90	-	-	47 ± 5.6	34	18	53 ± 8.6
120	60	11	-	-	-	-
180	60	9	18 ± 5.1	30	5	17 ± 6.9
300	-	-	15 ± 4.7	20	2	10 ± 6.8

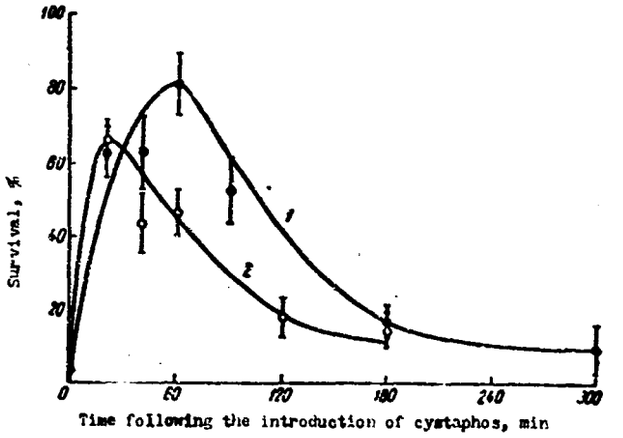

Fig. 49. Dependence of the anti-radiation effectiveness of cystaphos on the period between its introduction and the irradiation in rats [dose of 900 rads (1)] and mice [dose of 700 rads (2)].

Just as in experiments with rats, the concentration of radioactive tagging in tumors of mice is less than in normal tissues; however, the difference between them is insignificant here. The sharp maximum of the spread of the protector in the tumor in this case is evidenced by the fact that the reason for the shown difference is not so much the characteristic of the blood circulation of the mice, as it is the specific character of the blood supply in the adenocarcinoma of the milk gland. We did not detect a substantial difference in the spread of the protector in spontaneous and primary-transplanted tumor.

Presented in Fig. 50 are the results of the measurement of radioactivity of tissues from rats at different periods following the introduction of P^{32}-cystaphos. As in the case of tagging with S^{35}, concentration reached a maximum between the first and second hours after introduction. However, the accumulation of phosphorus proceeds in another way, than sulfur. This is evident from Fig. 48, where the relative change in the concentration of both taggings in the organs of rats is shown. As it appears, from 30 to 60 min after introduction of P^{32} into the animal it continues (at the same rate as in the first 30 min) to accumulate intensively in the tissues, whereas the spread

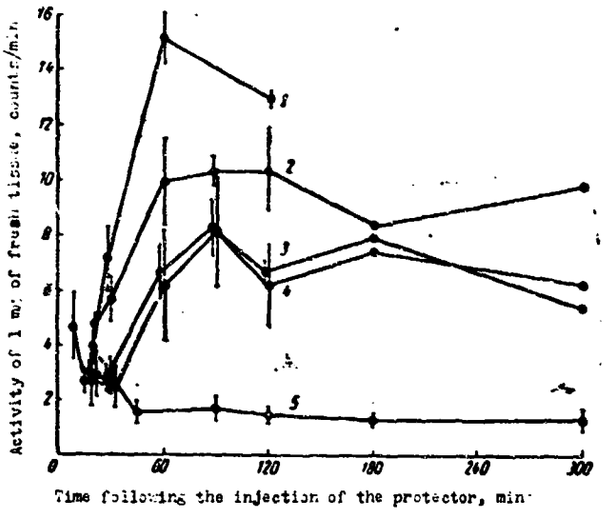

Fig. 50. Change in radioactivity of the various organs of rats after the injection of P^{32}-cystaphos: 1 - liver; 2 - bone marrow; 3 - intestines; 4 - spleen; 5 - blood.

of sulfur has already slowed down sharply. The revealed difference, apparently, means that the dissemination of cystaphos with the liberation of orthophosphate begins in the organism of an animal immediately after the introduction.

The obtained data still does not allow one to evaluate the portion of cystaphos, which has decomposed at some instant of time following introduction. However, the considerably greater duration of anti-radiation effectiveness of cystaphos (see Fig. 47) in comparison with MEA is evidenced by the rather long period of its conversion in the organism. The conclusion about the rapid dissemination of phosphate is confirmed by the difference in the relationship of concentrations of P^{32} and S^{35} in separate organs. It is known that P^{32} accumulates in a greater amount in the liver of rats and mice, than in other internal organs, which is not observed in relation to S^{35} [753]. This regularity is also characteristic in our experiments (see Figs. 46 and 50).

The obtained data provide a known perspective for the practical utilization of cystaphos in the therapy of tumors. At the same time they indicate the need to record a number of factors, which substantially affect the investigated effects. The characteristics of the blood supply of the tumors, governing their localizations and hystological nature, are related to their number.

One ought to emphasize that the described dynamics of the spread of a protector, specifically, the time when nearing the maximum, is characterized only by the prescribed means of introduction of the given species of animals, and can be something different with a change in the conditions of the experiment.

Cystaphos as a Means of Increasing the Effectiveness of the Chemotherapy with Alkylating Compounds

At the beginning of the chapter the expediency was mentioned of research on sulfur-containing protectors with intoxications by alkylating compounds for the subsequent extrapolation of the obtained data for conditions of radiation exposure.

Chloroethylamines are typical representatives of alkylating substances, clearly reproducing the basic radiobiological effects, and are, therefore, the named radiometric agents [754-757]. They suppress mitoses [758-760], possess cytotoxic properties [761, 762] and mutagenic activity [763-766], cause injury hemopoiesis typical for an acute radiation syndrome [101, 250, 251, 755, 768-770], intestines [755, 760, 775], gonad and embryos [776-778], destroys nuclein metabolism [755, 771-774] and cause the other pathophysiological and morphological changes in active proliferating tissues [755, 779, 780].

Despite the difference in the action of chlorethylamines and ionizing radiations, revealed in model systems [781] and during the cytogenetic analysis [782-786], as well as the differences in the absence of the oxygen effect in chlorethylamines [782], it is impossible to deny the fundamental similarity of the effects, which lie beyond the scope of simple phenomenological identity. We along with

R. G. Kostyanovskiy detected the striking analogy in the effects of both agents in 1958 during a comparative analysis of the biological effect methyl-bis-(β-chlorethyl)amine (embichine) over a wide range of doses [787]. Presented in Fig. 51 is the dependence of the average life span of mice on the amount of introduced embichine in comparison with the known data from Rayevskiy relative to X-rays [788]. Both curves converge at a point, corresponding to the minimum absolutely lethal doses of X-rays and embichine (750 R and 4 mg/kg).

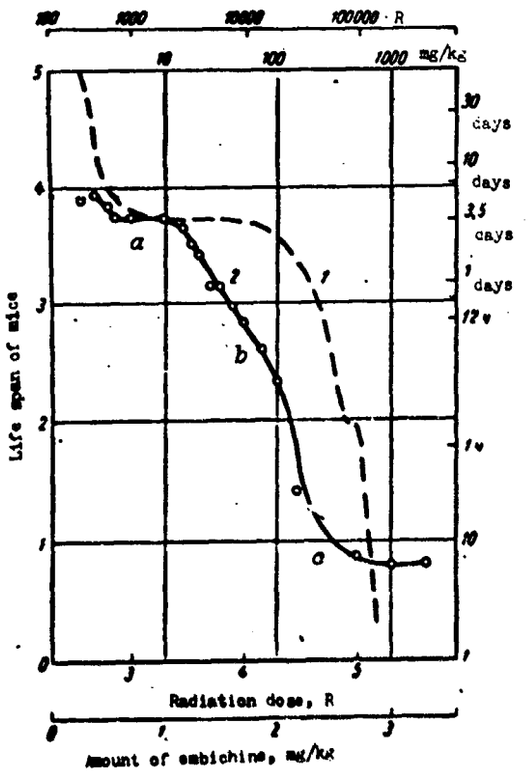

Fig. 51. Dependence of the average life span of mice on the radiation dose (1) [788] and on the amount of introduced methyl-bis-(β-chlorethyl)amine (2). Double logarithmic scale.

Even a cursory comparison of both curves does not leave doubts about the proximity of the reflected phenomena. The independence of the life span for the effect of embichine is also characteristic based on the introduced amount up to 15 mg/kg - plateau on the curve (segment *a*), the interval of progressive shortening of life of 15-100 mg/kg (segment *b*) and, finally, the range of doses of 100-2000 kg/kg,

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at which death approaches practically instantly (segment *c*). In this case at each of the shown intervals the clinical manifestations of intoxication are analogous to the corresponding disorders, characteristic for radiation defeat, induced by different radiation doses. In the plateau region the symptomatics are developed only at the 2nd-3rd twenty-four hour period and are characterized by the injury of hemopoiesis and of the intestines. At the interval of 15-100 mg/kg, death approaches with the phenomena of sharp disorders of the nervous system (oppression alternating with cramps). At the interval of 100-2000 mg/kg injury increases quite sharply and manifests itself in sharp spasms, which spread immediately following exposure and leading to death after 10-30 min (analogously "death by a ray"). Our attention shifts completely to curve 2 on the left which is the result of the accelerated transfer of intoxication in comparison with radiation sickness, and also the shorter initial rise, governed by the preferential injury by embichine of the intestines, associated with just how animals fail to live ahead of the allotted time, characteristic for the death from injury due to hemopoiesis.

The most convincing evidence of the generality of the mechanism of effect of ionizing radiation and chlorethylamines was gained during the test of a number of thiols protectors, which were also being made equally effective under conditions of radiometric intoxication. The results of the first investigations in this direction are presented in Table 57 [250].

In returning to the history of the discovery of the protective effect of MEA, one ought to keep in mind that the assumption about the expediency of the test of the given compound as a radioprotector was expressed by Bacq [789] on the basis of an analogous radiation effects of yperites and, specifically, in connection with the data on the protection of cholinesterase from yperitic injury by certain amines [790].

In model experiments, which include the investigations on bacteria [791] and tissue cultures [792], and in the numerous investigations

Table 57. Comparative data on the protection of thiols protectors with respect to irradiation and the effect of radiometric agents at minimum absolutely detailed doses.

Protector	Type of exposure	Mice			Rats		
		Number	Survived at the 30th 24 hour period		Number	Survived at the 30th 24 hour period	
			No.	%		No.	%
MEA	Irradiation	30	21	70	25	18	72
	Embichine	30	20	67	20	18	90
	Trichlorotriethylamine	-	-	-	25	20	80
Cystamine	Irradiation	30	18	60	20	14	70
	Embichine	20	10	50	20	9	45
AET	Irradiation	35	32	91	20	10	50
	Trichlorotriethylamine	30	24	80	-	-	-
Control	Irradiation	30	2	7	36	2	6
	Embichine	30	1	3	20	1	5
	Trichlorotriethylamine	-	-	-	25	-	0

Note. MEA, cystamine and AET were injected intraperitoneally over a period of 15 min prior to exposure to the amount of 150 and 100 mg/kg per mouse and rat, respectively.

on mammals including dogs [793] the protection by the many thiols protectors from various chlorethylamines was demonstrated.

Great majority of the investigations was made using embichine; the protection with the help of cysteine [794-802], MEA or cystamine [800, 803-808], thiophosphate [809] thiosulfate [785] and sodium diethyldithiocarbamate [774] and AET [181, 802, 810-815], was shown. Furthermore, the weakening of the intoxication with Dopane was attained by the introduction of MEA [816] and AET [817], but the weakening of intoxication by endoxan - cysteine [800, 818], MEA [800, 819, 820] and AET [800, 817].

The actual mechanisms of protection by thiols protectors from chlorethylamines exist; immediate alkylation with the interaction of chlorethylamine with molecules of the protector, and the blocking by

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the most damaged cellular structures. Favoring the second assumption [798, 799, 801-811, 821] as evidence are the data about the absence of the protection upon the simultaneous introduction of the protector and embichine [794, 808], as well as the data about the value of the spatial configuration of the protective compounds: high effectiveness of the *l*-isomer of racemate on cysteine and the low *d*-isomer [798, 799]. The hypothesis [799] was also introduced based on this for the fundamental possibility of weakening the leukopenic effect of embichine without substantially weakening the antitumorigenic effect, taking into account the biochemical differences of the normal and tumoral cells.

The results of the research of the effect of protectors on the anticancerous activity of chlorethylamines is not unique. Based on the data of Japanese researchers, cysteine weakens both leucopenia, induced by nitrosin [Translator's Note: nitrosin not listed in chemical dictionaries. Based on similar terms, suggested transliteration is given , and the suppressing effect of the latter on the growth of Yoshida sarcoma in rats [797]. According to the data from A. B. Syrkin, MEA at a dose of 100 mg/kg retards anticancerous effect of dopane, but at doses of 10-20 mg/kg it has an effect on the latter, by weakening the leukopenic effect [816]. AET, by reducing the toxic effect on Erlich's carcinoma and Gardner's lymphosarcoma which was not observed in Krebs' carcinoma and Dalton's thymoma [812].

It is obvious, as already mentioned, the possibility of differentiated protection of normal and tumoral tissues can be determined by a series of factors, pertaining to both the specific character of the tumors, and to the conditions of application of the protectors. In any case in certain experimental investigations such an effect has been shown rather clearly [181, 800, 810, 817-822].

Having correlated our own data on the selective distribution of cystaphos between tumoral and normal tissues, we then studied the possibility of its utilization in the chemotherapy of tumors.

Utilization of Cystaphos on Experimental Chemotherapy of Tumors

In works, carried out by R. G. Aliyevoye and others [712, 823], it is shown that the introduction of cystaphos intraperitoneally shows a marked protective effect, forewarning the death of 25-100% of the mice and rats subjected to the fatal intoxication of embichine or endoxan (Table 58).

Table 58. Effect of the preliminary introduction of cystaphos (350 mg/kg) on the survival of animals, having received a lethal dose of the alkylating compounds.

Dose of the preparation, mg/kg	Interval between the introduction of cystaphos and alkylating compounds, min.	Mice		Rats	
		No. of animals	Survival, %	No. of animals	Survival, %
Embichine, 5	2-3	60	25	-	-
	15	10	80	-	-
	30	10	80	-	-
	60	10	70	-	-
	Control	60	12	-	-
Endoxan, 500 for mice, 240 for rats	15	130	95	50	72
	30	30	73	-	-
	60	10	30	-	-
	Control	81	1	36	3

The degree of the protective effect with exposure to endoxan diminished with the time elapsed following the injection of the protector. With the intoxication of embichine the protection was practically absent at an interval of 2-3 min and it was well expressed in the course of 15-60 min. The results of these experiments is easy to explain, if we take into account the structural features and the pharmacodynamics of the shown compounds associated with them. The transformation of cystaphos into the active form is associated with the certain time of discovery of the thiols group as a result of fermentative hydrolysis [751-752]. Fermentation activation of endoxan occurs over 2-4 h [819, 824, 825]. Embichine alkylizes immediately after introduction; therefore, the realization

of protection from it requires one to know its high concentration in the active form of a protector in the organism. Considerations about the value of the carrier form of cystaphos and endoxan were confirmed by the results of experiments, in which for the first time the possibility was shown for lowering the toxicity of the alkylating compounds by the subsequent and not by the preliminary introduction of the protector, such as we have shown independently and simultaneously in the example of endoxan and MEA [819] or with cysteine [818].

As can be seen from Table 59, the introduction of cystaphos even immediately following the injection of embichine did not prevent the death of animals, while from the effect of endoxan a high protective effect could be achieved in rats over the course of 30 min, and in mice even over 1 h following the introduction of the protector.

Table 59. Survival of animals upon the introduction of cystaphos (350 mg/kg) following exposure to alkylating compounds.

Dose of the preparation, mg/kg	Interval between the introduction of the alkylating compounds and cystaphos, min	Mice		Rats	
		No. of animals	Survival %	No. of animals	Survival %
Embichine, 5	1-2	30	0	-	-
	Control	20	0	-	-
Endoxan,	10-15	104	91	30	80
500 for mice,	30	10	90	10	70
	60	110	74	-	-
240 for rats	Control	73	12	16	6

Obtained results, as well as the broad spectrum of antitumorigenic effect of endoxan, made it possible to concentrate on the further research for the feasibility of increasing the effectiveness of chemotherapy by means of using increased doses of endoxan under the protection of cystaphos. The experiments were conducted on a model of solid tumors of M-1 sarcoma in rats and Erlich's carcinoma of mice, which themselves are relatively resistance with respect to endoxan; the latter at therapeutic doses (7-8 mg/kg) impedes the growth of M-1 sarcoma up to 35-50% [826], and Erlich's carcinoma up to 46% [827].

M-1 sarcoma was innoculated in the skin of the femur in the form ellular pulp, containing approximately $2 \cdot 10^8$ cells, and Erlich's inoma - by subcutaneous injection of 0.3 ml of ascitic liquid.

The data in Tables 60 and 61 provide evidence that the utilization ystaphos allows the use of single or repeated massive doses of xan, resulting in the death of 80-100% of the control, of the otected animals. In this case along with protective effect 80% of the survival of the experimental animals) a complete lution of the tumor is observed. It is important that the pro-ive effect of cystaphos is maintained over the range of 100-350 g, as evidenced by the considerable latitude of the therapeutic ct of the protector. With repeated injections of large quantities ndoxan there is an accumulation of toxicity, which diminishes with ncrease in intervals between introductions.

le 60. Results of experimental therapeutics of Erlich's carcinoma endoxan under the protection of cystaphos.

of the preparation, mg/kg	No. of mice	Survival at the 30th 24 h period, %	Retardation of the growth of the tumcr, %
oxan, 500 [control]	20	0	-
taphos, 350; Endoxan, 500	20	70	100
taphos, 175; Endoxan, 500	10	60	100
taphos, 100; Endoxan, 500	10	50	100
oxan, 250 (3 times at inter-ls of 10 days) [control]	10	20	-
taphos, 350; endoxan, 250 times at intervals of 10 ys)	20	75	100
taphos, 175; endoxan, 250 times at intervals of 10 ys)	20	60	100

Note. Cystaphos was injected 15 min prior to the injection of endoxan; therapy began from the 5th twenty-four h period following the inoculation of the tumor.

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Table 61. Results of the therapy of M-1 sarcoma with endoxan in large doses under the protection of cystaphos.

No. of the experiment	Dose of the preparation, mg/kg	No. of rats	Survival at the 30th 24 h period, %	Retardation of growth of the tumor, %
1	Endoxan, 240 [control]	40	2.5	-
	Cystaphos, 350; endoxan, 240	50	70	100
	" 175 "	10	70	100
	" 100 "	10	70	100
2	Endoxan, 80 (4 times at intervals of 5 24 h period) [control]	40	2.5	-
	Cystaphos, 350; endoxan, 80 (4 times at intervals of 5 24 h period) [control]	20	80	95-100
	Cystaphos, 150; endoxan, 80 (4 times at intervals of 5 24 h period) [control]	30	63	100
3	Endoxan, 100 (3 times at intervals of 5 24 h period) [control]	10	0	-
	Cystophos, 350; endoxan 100 (3 times at intervals of 5 24 h period) [control]	10	50	100
4	Endoxan, 100 (3 times at intervals of 10 24 h period) [control]	10	40	100
	Cystaphos, 350; endoxan, 100 (3 times at intervals of 10 24 h period)	10	60	100
5	Endoxan, 100; (3 times at intervals of 10 24 h period) [control]	30	47	100
	Endoxan, 100; cystaphos, 350 (3 times at intervals of 10 24 h period)	90	90	100

Note. Therapy they began from the 8th twenty-four hour period following inoculation of the tumor; in experiments numbers 1-4, cystaphos was introducted 15 min before endoxan, and in experiment No. 5 - 15 min following it.

The application of endoxan in large doses at wide intervals under the protection of cystaphos made it possible to obtain the complete resolution of M-1 sarcoma at the beginning of the therapy even at the 15th 24 h period following inoculation, when the weight of the tumor attained 10-20 g (Table 62). The application during these twenty-four hour periods of smaller doses of endoxan (40 mg/kg) is less effective; in this instance it causes only an insignificant retardation of the growth of the tumor in comparison with the untreated control (experiment No. 2). Cystaphos did not weaken the antitumorigenic activity of endoxan, by facilitating the increase in the survival, possibly, as a result of the removal of the toxic effect, which is required under these experimental conditions with intoxication, induced by the rapid growth of the tumor, and results in the death of the majority of the control animals at the 30th twenty-four hour period.

Table 62. Results of therapy of M-1 sarcoma from the 15th twenty-four hour period following inoculation and upon the introduction of cystaphos 30 min after that of endoxan.

No. of the experiment	Dose of the preparation, mg/kg	No. of rats	Survival at the 30th 24 h period, %	Retardation of growth of the tumor, %
1	Endoxan, 100; cystaphos, 350 (3 times over 10 24 h period)	20	20	95-100
2	Endoxan, 40 (3 times over 10 24 h period), [control]	20	8	35
	Endoxan, 40; cystaphos, 350 (3 times over 10 24 h period)	20	16	40

The differentiated protection of normal tissues without weakening the antitumorigenic effect was also established by other researchers, who used AET [817] and MEA [816, 819, 820] in experimental therapeutics with dopane and endoxan. The weakening of the toxic effect of endoxan and embichine and the increase in the life span of rats with spontaneous lymphatic leukemia was shown under the influence of AET, cysteine and MEA [800].

Effect of Mexamine on the Oxygen Concentration in Normal and Tumoral Tissues

Earlier it was mentioned that except for the selective distribution of the protectors on their differentiated action, other factors can also be effective. Specifically, one can assume that inasmuch as the aeration of normal tissues is higher than of tumoral ones, the effect of protectors with a hypoxia mechanism of effect in normal tissues will be large [748]. Furthermore, it is entirely possible to also expect a different degree of vasoconstrictive effect in the tumors as compared to the degree of the vasoconstrictive effect in normal tissues.

All this was conducive for us to evaluate experimentally such a possibility for mexamine. For this purpose Yu. I. Rampan made polarographic studies of the dynamics of the level of oxygen concentration in the organs and tumors of rats from primarily innoculated Sarcoma-45 under the influence of mexamine (intraperitoneally injected with 3.5-15 mg/kg). Using the multichannel recording of the effect, level of oxygen concentration in organs and tumors was determined simultaneously.

It turned out that immediately following the introduction, mexamine causes the lowering of the oxygen content in the subcutaneous cellulose, spleen and bone marrow, continuing for 30-90 min. In the tumor hypoxia is developed more slowly, and it is considerably less expressed.

At present the degree of change in the radiosensitivity of the skin and in the tumor under the influence of mexamine is being studied by comparative aspect, and analogous experiments on dogs with spontaneous tumors have been started.

The disclosed effect of mexamine on the level of oxygen concentration along a favorable trend for radiation therapeutics is evidenced by the possibility, in principle, of the directed pharmacodynamic change in the oxygen status in tumors and critical tissue which holds

promise for the practical application of corresponding protectors.

The obtained experimental data makes it possible to proceed with clinical tests on cystaphos and mexamine.

Tolerance of Cystaphos and Mexamine to Man

As already indicated, some of serious obstacles in the way of the utilization of protectors on man is their high toxicity. According to Bacq, people can adequately tolerate MEA at doses up to 400 mg; at doses of 500-1000 mg acute amaurosis appears [69]. V. S. Vakhtel' and L. F. Sinenko [717], having applied cystamine at the rate of 200-800 mg in roentgenotherapy, only noted individual complaints about unpleasant sensations without any objective changes in the blood pressure and urine. During the investigation of the tolerance to cystamine in healthy people [9, 12] it was established that doses of 600-800 mg are adequately tolerated; only 9-10% of those investigated noted acute unpleasant sensations (heaviness in the head, dizziness, weakness, nausea). The same doses of preparation in oncologic sick people brought on complaints of nausea, heartburn and heaviness in the epigastric area in 30% of the cases, treated following food intake [9, 12].

AET upon the intravenous introduction caused an acute reaction in the form of nausea, vomitings, coughing, sense of burning in the eyes, "congestion" of the head, in connection with how much of a dose to use when limited to within 10-15 mg; all the patients, receiving more than 500 mg of the preparation internally, complained of nausea, and after 750-1000 mg vomiting occurred [827a]. Analogous phenomena were observed also by other researchers at doses of AET of 400-900 mg [828, 829]. At the same time Slosser reports that sick cases tolerate 1000 mg of AET with a minimum of toxic effect [830].

Thus, the human, obviously, can internally accept more than 1000 mg of AET, MEA or cystamine, i.e., more than 15 mg/kg. Among all these the radioprotective effect of these preparations in mice upon oral introduction is observed at doses of 400 mg/kg, which exceeds by 25 times the doses, tolerated by man.

Information on the clinical tests of indolylalkylamines until recently was limited to one piece of research, in which it was noted that mexamine at a dose of 50 mg, applied to weaken radiation reactions with γ-therapeutics, had caused these or other side phenomena (nausea, vomiting, dizziness, pain in the stomach, racing of the pulse) in 9 of the 45 sick cases [831]. In this case one-half of the cases managed to rid themselves of the already developing manifestations of radiation reactions and even a third - the weakening effect, outside of that depending on whether or not, the preparation was applied before or after irradiation.

We studied the tolerance of mexamine and cystaphos in hopes of finding subsequent use for it in radiation therapeutics, and cystaphos - also in the chemotherapy of tumors.

Dispeptic disorders can be caused by the irritation of the gastric mucosa; therefore, the various ways of introducing the preparations were studied. Cystaphos in the form of a tablet taken internally, and in solution - intramuscularly as well as by enemas; mexamine - in the form of a lozenge taken internally and in the form of suppositories in the rectum. Rectal application of protectors was substantiated by us earlier in special experiments, which revealed the high effectiveness of the protection by such a means of introduction [705].

Cystaphos was tested on 78 sick cases, 60 of them took it in the form of tablets, and 18 were injected intramuscularly or in the form of an enema.

It was explained that the absolute majority of the sick patients freely tolerated the intake of cystaphos up to 3 g, and by enema and intramuscularly up to 2 g. Only in a single sick person nausea occurred, which already arose after the intake of 1.5-2 g of preparation which testifies to individual raised sensitivity. Consequently, a human tolerates cystaphos at a molar ratio of double that of AET, MEA or cystamine.

During the rectal application of cystaphos irritational symptoms of gastric mucosa of the rectum were not noted.

It is very important that local reactions including pains were not observed pains, using intramuscular injection of the preparation. This confirmed the experimental data on the absence of irritation at the spot of introduction in animals [387].

As a side reaction upon the introduction of cystaphos one ought to make note of the increase in the temperature up to 37-38°C, which was observed in 60% of the sick cases over 2-8 h following injection.

During the first stage of the clinical study of mexamine 42 men were under observation; they took the preparation repeatedly (4-10 times) internally (in the form of lozenges, 50 and 100 mg in weight) and 11 took the preparations in the form of suppositories, which contained 50 and 100 mg of mexamine. The side reactions in these cases, in the form of nausea and dizzinesses, were noted only in a single sick patient (a total of 6 men), aside from depending on the dose of preparation.

Suppositories did not cause irritation of the rectum.

The obtained data, as well as the results of the works of R. B. Strelkov [868], having shown the possibility of the free utilization of up to 500-700 mg of mexamine by man (from the preliminary premedication by intake of 50 mg of mexamine 30 min before the basic dose), compelled us to further development of the investigations. For this purpose the author at first on behalf of colleagues V. S. Shashkov and N. N. Suvorov, and later on together with I. A. Romanenko and A. Ye Vermel in a clinic using 120 sick cases did not only confirm the data, obtained by R. B. Strelkov [868], but also showed the adaptability of mexamine at the same doses without certain premedication. Except for the mentioned subjective unpleasant sensations (in individual investigated cases - vomiting) some sort of objective disturbance (changes in the temperature, pulse, arterial pressure, EKG, EEG and changes in the status of the peripheral blood) did not take place.

At the same time Yu. I. Rampan by the method of polarography

detected that for 30-40 min following the intake of 500-600 mg of mexamine in subcutaneous cellulose, the level of oxygen concentration was reduced up to 20-25%, similar to that observed during the polarographic analysis of muscles [868].

Thus, one succeeded in approximating to a maximum the doses of mexamine, easily tolerated by man (7-8 mg/kg taken internally), radioprotective doses for mice (7-10 mg/kg parenterally).

Application of Cystaphos in the Clinic for Therapy Using Endoxan for Cancer of the Milk Gland

Cancer of the milk gland was chosen as a clinical model in connection with the data about the effectiveness of endoxan on this illness [832-836], and also taking into account the possibility for a suitable visual estimate of the results of the therapy.

In the majority of investigations, associated with the utilization of endoxan, a daily application of 100-300 mg is recommended to lower the number of leucocytes not lower than 3000 per 1 mm^3 (a running dose of 5-9 g).

At the same time in accordance with the experimental data of Druckrey and coworkers [824, 825, 837] the repeated introduction of small doses of endoxan results in the preferential cumulation of the toxic effect as well as to the appearance of resistance in the tumoral tissue. In their opinion, the therapeutic effect of endoxan is a function of its concentration at a given moment, and that is why they recommend the introduction of large single doses of endoxan at corresponding intervals in order to even out the cumulative effect.

Also, other researchers [832, 834-836, 838] indicate it is expedient to increase the single doses of the preparations.

There have been no attempts to apply the protectors to chemotherapy, if we exclude the unique work, in which the attempt was made to use cysteine in the treatment of bronchogenic carcinoma with endoxan which allegedly diminishes the development of leucopenia [839].

The possibility of increasing the effectiveness of the chemotherapy by a gradual increase in the single doses of endoxan was studied by R. G. Aliyev in the surgical division of the Institute in the name of Gertsen using 31 patients with breast cancer in the III and IV stages. Twenty-four of them were injected with endoxan following a preliminary (15-20 min) intramuscular injection of cystaphos. The material of these investigations was comprehensively described in a monograph [840]. Here, let us speak only about their basic results.

The application of large doses of endoxan caused a remission or a considerable objective improvement in the condition of 27 patients of the 31 (Table 63).

The duration of the objective improvement was monitored on 4 patients over the course of 3 months, on 2 patients - 5-6 months, on 10 patients - 7-8 months, on 13 sick patients - up to 1 year or more. The complete regression of the tumors or of metastases made it possible to complete the radical operation.

However, not in one case did the therapy appear radical, since subsequently patients returned with a relapse of tumor which is also understandable, if we take into account the contingent of patients who have long since suffered by a process, not subject to any other methods of therapy.

The limited number of patients excludes the possibility to analyze the dependence of the effect on a single dose of endoxan. But during the comparison with the results of therapy by lesser doses of endoxan noticeable difference in the effect (Table 64) was seen which provides evidence of the indubitable expediency of the application of large single doses of endoxan.

The effectiveness of cystaphos, both in relationship to the weakening of the overal toxicity of endoxan, and in relationship to its antitumorigenic activity is most intricate to evaluate. From the examination of material in Table 64 it is not possible to notice any differences between the results of therapies of the patients who

Table 63. Results of therapies of sick cases using endoxan in the large doses during the preliminary application of cystaphos.

Table 63. Results of therapies of sick cases using endoxan in the large doses during the preliminary application of cytaphos.

Group of sick cases	Preparation	Single dose of endoxan, g	No. of injections and the intervals between them, days	Cumulative dose of endoxan, g	No. of sick cases				Remarks
					All	Complete disappearance of tumors or of metastasis	Partial resolution of tumors; absence of data about metastasis	Absence of data about the metastastic spreading for not less than 3 months	Continuing growth of the tumor (without effect)	
1	Cytaphos + endoxan	2	4 times over 7-10 days	10	10	-	8	-	2	30 min prior to injection of the basic dose into patients taking 1 g of cytaphos internally. In the absence of a reaction, 3 g of ampoule-form preparation taken intramuscularly in 20 ml of 0.5% solution of novocaine.
2	Cytaphos + endoxan	3	4-9 times over 9-10 days	12-27	9	1	6	1	1	
3	Cytaphos + endoxan	5	3 times over 8-10 days	15	5	1	4	-	-	
4	Endoxan	2-3	8-9 times over 7-10 days	9-12	7	1	6	-	-	15-20 min of jet injection in the cubital vein using endoxan at the rate of 100-150 ml of 5% solution of glucose

Table 64. Results of the therapy on breast cancer using endoxan according to published data (citation on [840]).

No. of patients	Dose of endoxan, g		Objective improvement		Source
	single	sum total	No. of patients	%	
100	0.2	6-8	36	36	Reov L. S. Med. J. Austral. 1, 686 (1961)
21	0.8-1.0	5-6	5	23	Lold L. Salvin G. Cancer chemother. Rep., 16, 413 (1962)
6	0.2	2-12	2	33	Lopes C. E. Cancer. chemother abstract, 463, (1963)
15	0.6-1.2	2.4	6	40	Wayne R. et al. Cancer chemother Rep. 16, 407, (1962)
in research not shown	0.2	6	-	50	Falkson T., Brit J. Derm. 72, 296 (1960)
27	2-2.5	2-2.5	7	26	Stoll B. A., Mater J. H. Brit. Med. J. No. 5247, 283 (1961)
18	0.2-1.5	1.8-30	9	50	Bromberg, V. M., Kundzinya, I. A. in the book "Cyclophosphan" Riga, 1965, str. 131.
18	0.2-1.0	1.8-18.5	10	55	Rosenbakh, V. P. id, page 177.
31	2-5	12-27	27	87	[840]

have taken cystaphos and those who did not take it. For the final estimate a further comparative observation is necessary. Among those "protected" by cystaphos those patients with a lower incidence developed certain side reactions (cystitis, diarrhea, agranulocytic angina), although the overall dose of endoxan on the patients was less than on those not receiving the protector.

No less important is the fact that on three of the 7 "control" patients hemostimulation (transfusion of blood and leukocytic masses)

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was performed, whereas everything that was "protected" (24) was terminated in the course of therapies with endoxan without hemostimulating measures. According to the degree of development of leucopenia the differences between "protected" patients and the sick patients, which were not to obtain a protector, were not detected. However, without the data of the cytogenetic analysis of the bone marrow, which unfortunately, was not conducted, it is not possible to evaluate the protection of the hemopoiesis.

By analyzing the results of the application of large doses of endoxan at wide intervals, it is possible to draw a conclusion about the indubitable expediency of such a scheme of chemotherapy, substantiating the experimental prerequisites [824, 825, 837] about the intrinsic endoxan of high cumulation of toxic effect and considerable reversibility of the therapeutic effect.

Clinical practice is limited only by the single purposes of large single doses of chemotherapeutic preparations, in general, and endoxan, specifically. In the work of A. M. Garin and others [838] also reported on the inclusion in the usual cycle of therapy of one-three injections of endoxan at doses of 1.5-2 g. In this case the authors did not see the expediency of increasing the single dose higher than 45 mg/kg (approximately 2 g). However, it is difficult to agree with this conclusion, because the intervals between application even at such doses were equal to 21-24 days. As a result the cumulative doses of endoxan higher than the accepted therapeutic doses (not more than 8 g) could not be increased.

As can be seen from the results of our work, even with the application of double large doses (3-5 g) the intervals between the injections did not exceed 10 days, and in this case, one succeeded in increasing the cumulative dose of endoxan to 12 g in the "control" patients as well as to 21 g in those having taken the cystaphos.

These data deserve fixed attention in the hopes of the possibility to substantially increase the effectiveness of the massed chemotherapy of patients with earlier manifestations of tumors. Furthermore, they

provide evidence for the need of detailed research on the reparational condition of tumoral tissue and organs of hemopoiesis depending on the amount of the single dose of radiometrics and intervals between its injections.

One cannot help but also consider the overall response of the organism of a cancerous patient, along with the possibility of the protection by the protectors whereby great significance in the outcome of chemotherapy is given. Therefore, even in the absence of direct information on the protection of hemopoiesis, the injury of which along with chlorethylamines in comparison with irradiation has its characteristics [842], the weakening of any side reactions acquires serious value. By this method the practical possibility of the fundamental estimate of the effectiveness of doses of thiols protectors tolerated by man, which, on solid grounds can be extrapolated under conditions of overall irradiation, are revealed.

As a matter-of-fact, such considerations were followed by the author, who included a fragment of the clinical investigations in the monograph, which one should consider only as preliminary data. However, these modest results are primarily the merit of a group of scientists of the Institute named after P. A. Gertsen headed by professors V. V. Gorodilov, V. M. Bergol'ts and A. P. Bazhenov and, of course, R. G. A' vev, to whom the author expresses his heart-felt gratitude.

Outlook for the Practical Utilization of Protectors

An analysis of experimental and clinical investigations, devoted to the research on the possibility of pharmaco-chemical antiradiation protection of man, shows that by this method the insignificant therapeutic latitude of the most effective compounds should be considered the most insurmountable obstacle thereby making the effectiveness of doses of these preparations tolerated by man as doubtful. However, from our viewpoint [7], there are no sufficient grounds for such pessimism, especially of late because the known perspective for overcoming this barrier has been outlined.

First of all this relates to pharmacological active compounds, whose doses per unit weight cannot be mechanically transferred from animals to man [137], considering the specific differences characteristic for these compounds.

Furthermore, the therapeutic latitude of indolylalkylamines is not all that small. Based on the data of R. B. Strelkov [868], the therapeutic index (ratio of LD_{50} to the effective protective dose) of mexamine is equal to 88 and 77 upon introduction under the skin or internally, respectively.[1] It also seems that man rather freely transports mexamine in amounts, close to that of the radioprotective doses for mice. They cause important reactions in the organism of man - for the realization of protection the lowering of the level of the oxygen concentration in the subcutaneous cellulose and muscles in the tissue.

Obtained data makes it possible to count the successful application of mexamine for increasing the effectiveness of radiation therapeutics of tumors taking into account the weakening of the skin reactions. The results of the experiments, as evidenced by the differential effect of mexamine on the level of oxygen concentration in normal tissues and transplanted tumors are quite promising. At present, we are conducting corresponding investigations using the polarographic analysis of the oxygen state in tumors, enclosing the tissues, lymphatic nodes, kin and bone marrow, which will make it possible to evaluate these possibilities.

More complex is the matter of the practical application of sulfur-containing compounds, whose effectiveness is associated with the need for determining the saturation of the cellular structure of radiosensitive organs by these compounds.

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[1]According to our datum, the therapeutic index of mexamine for mice, depending on the duration of the protective effect, constitutes 8-40 and 10-30, respectively, upon introduction internally or intraperitoneally.

Nevertheless, one cannot altogether agree with the categorical negation [868] of the feasibility of the practical application of sulfur-containing protectors, especially since the known perspectives for them were recently outlined.

First, the contemporary state of knowledge does not allow one to completely deny the value of the pharmacological reactions, caused by aminothiols. Moreover, in the radioprotective effect of cystamine and AET the presence of a pharmacological component will not be subject to doubt, and even if unknown, as having specific value for man, especially when considering the successful application of the mixture of protectors on dogs [407, 437].

Secondly, the synthesis and testing of aminoalkylthiophosphatic compounds showed the practical possibility of obtaining less toxic and more effective (in equimolecular calculation) protectors.

One of them is cystaphos, whose therapeutic index on mice is equal to 6, whereas the therapeutic index of MEA and AET amounts to 2-3; furthermore, man easily tolerates cystaphos in the amount of 40 mg/kg internally or 30 mg/kg intraperitoneally which is 8-12 times less than the radioprotective doses for mice using the same methods of introduction.

Finally, recently an extremely interesting communication from Akerfeldt and others [869] appeared about the synthesis and testing of new compounds of this class, having a high radioprotective effect at doses, which is 10-20 times less than the concentration of MEA in the calculation for equimolecular concentrations. For example, the highest effect (FUD = 2.3) [FUD] (ФУД) diminishing dose factor of diammonium salt of amidothiophosphoric acid manifested itself upon introduction into mice using 0.02 mg/g, or 0.14 μmole/g, whereas, equimolecular dose of MEA, according to [869], amounts to 2.1 μmole/g (FUD = 1.84).

Consequently, for the first time the possibility was shown of obtaining a high radioprotective effect using sulfur-containing

protectors in amounts, comparable with doses of such pharmacological active compounds as serotonin. Notwithstanding this case before us is an example of how important the practical relationship is in the complex mechanism of protection: pharmacological and the cellular-concentrational.

The methods of estimating the effectiveness of protection of man being applied at present are inadequate for the given assignment. It is necessary to use others, advisably quantitative criteria. One of them consists of the cytogenetic analysis of the bone marrow during total irradiation corresponding to share of patients or in the same investigation of the bone marrow of a section, directly subjected to irradiation with regional exposure. For compounds with a pharmacological mechanism of effect, specifically indolylalkylamines, the methods of estimating radiation injury of the skin are available and deserve attention.

Another means of solving the same problem consists of an attempt to weaken the intoxication, induced by radiometric compounds of the alkylating type with the aid of thiols protectors, whose protection has repeatedly been shown under experimental conditions.

The proposed methods have been developed and have been perfected by us recently, and the first results of the corresponding investigations are quite encouraging.

Conclusion

From a critical aspect the intrinsic and source material for the feasibility of the practical utilization of protectors for the protection of man have been examined. It was shown that the results of corresponding experimental and clinical investigations until recently provide grounds for the solution of the given problem neither in a positive nor a negative sense. Unfortunately, it is impossible to recognize the satisfactory and available information on the utilization of protectors in radiation therapeutics, which is radically distinguished from the conditions of radiation exposure, where the protective effect in the experiment is disclosed.

Recently the known perspective for the practical utilization of individual protectors - indolylalkylamines, specifically mexamine, and sulfur-containing alkylphosphates were outlined. For an objective estimate of such a possibility adequate quantitative criteria of the immediate injury of the critical organs must be used.

The successful solution of the given problem requires complex and meaningful work of experimenters and clinical workers in the new field of applied radiobiology - clinical radiobiology, which is founded on the basis of these efforts.

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RESULTS AND PROSPECTS OF THE INVESTIGATIONS

In accordance with the presented experimental material two principally different trends in the investigations in the field of the artificial change in the radioresistance of an organism, stand out.

1. The estimate of the possibility of the practical utilization as a means of protection and for early therapeutics.

2. Research on the dependence of radio sensitivity on the condition of irradiation in connection with problems of radiation therapeutics and radiation-hygienic problems.

Stimulation of Proliferational Activity of the Bone Marrow – One of the Promising Trends in Protection and Early Therapeutics of Radiation Damage to an Organism

The book presents numerous eviden[illegible]e leading role of antiradiation protection as a mechanism (within a definite range of doses) of generating background of the valuable hemopoiesis cells, comprising the source of accelerated regeneration. This condition maintains its leading value even with the fractionated irradiation aside from depending on a single (nonlethal, slightly- or moderately lethal) doses. Diminishing dose factor [FUD] (ФУД), measurable, for example, based on the total number of karyocytes of the bone

marrow, correlating with the degree of increase in the survival of animals, therefore can serve as the quantitative criterion of protection.

It is natural that the increase in the proliferating background should inevitably have a favorable effect on the protection which, on the whole, is also observed with an increase in the amount of FUD of the protectors, for example, during its combined application.

At the same time we established that the leading component of the initial devastation of the bone marrow is the retardation of cellular division and the continuing ejection of form elements in the bloodstream. Consequently, the reduction in time of the mitotic unit should also facilitate an increase in the sizes of the original background of vital cells.

It is very important that such an effect, in principle, can produce intervention following irradiation.

Recently the protection was shown in rats (39% survival) and guinea pigs (60% survival) at absolutely lethal doses (800 and 550 R, respectively) with the introduction of derivatives of adrenaline over a period of 5 min following the irradiation [843]. In the same type of animals has been detected not only a preventive effect, but a therapeutic effect of bacterial lipopolysaccharides [844]. Unfortunately, a cytological investigation of the bone marrow in this instance was not conducted. Finally, the therapeutic effect of the high polymer, [DNK] (ДНК) deoxyoribonucleic acid deserves attention [845, 846], which, as the authors show, is clearly associated with the beneficial effect on the earliest cellular manifestations of injury to hemopoiesis, including the suppression of mitoses.

Along with the search for various preparations, having such features, there is also another way to increase the effectiveness of protection. It consists of the research on the possibility of autotransplantation of the bone marrow in protected animals.

G. S. Strelin and coworkers [189, 847-849] showed the considerable increase in the survival of animals using protection and the subsequent autotransplantation of the bone marrow from the protected section.

Many researchers have observed the sharp intensification of the protective effect in the protectors during the subsequent transplantation of homo- or isologous bone marrow [14, 181, 235, 580, 850-854].

The fact of the dispersal of transplanted cells in this case, which with the repopulation itself, can serve as a source of progennic precursors of DNK for the remaining vital cells and, consequently, facilitate the formation of many origins of hemopoiesis. As the experiments on mice showed, the protection of many sections of the body results in a substantial activation of hemopoiesis [23, 464, 465, 855, 856], especially in combination with the preliminary injection of the protectors [857, 858], effective doses of which in this case were considerably reduced [857]. However, the exceptional lability of the cells of the bone marrow characteristic to mice [855, 856], is not observed in other species of animals nor in man. Therefore, the effect of autotransplantation in mice is also expressed in a considerably lesser degree than in rats and monkeys [848, 859], because the dispersal of the hemopoietic cells from the protected sections of the mice proceeds intensively even in the first minutes and hours following irradiation [855, 856].

There is reason to believe that autotransplantation for the remaining species of animals should be effective both in the case of the application of protectors (as a result of preserving the vital protected cells), and simply at moderately lethal doses, having in mind the effectiveness of the transplantation of partially irradiated bone marrow [848, 859], and bone marrow following exposure to yperite [860].

All this is handled very expediently by conducting corresponding experimental investigations, especially in hopes of successfully

developing the application of protectors in massed radiation therapeutics and in a chemotherapeutical clinic, because transplantation and autotransplantation of the bone marrow itself are already used as a means of diluting the induced radiometrical agents [861, 862] and diluting the irradiation [863] of the aplasia of hemopoiesis.

The most successful appears to be the combination of autotransplantation with methods, stimulating the cellular division (during the earliest periods), probes and tests which should be, in our opinion conducted in the most intensive fashion.

Problem of Protection Using Small Doses of Irradiation

In research the illegality of generalized statements about the ineffectiveness of chemical protection with the lowering of the dose of irradiation has been shown. In any case over the range of doses, which cause apparent injury of hemopoiesis, the protection of the latter manifests itself rather clearly.

At the same time little is still known about the feasibility of protection of the organism at lower doses. At sublethal doses of irradiation the "protected" animals, which have survived the usual 30-day period of observation, seem weakened and just as the "unprotected" controls, die more frequently intact in the succeeding periods. Consequently, one quantitative completion of the proliferational pool of the bone marrow is insufficient to fully characterize the restoration of the organism. Obviously, at sublethal irradiation there remain weakly or entirely unprotected (most likely because of the high radiosensitivity) certain cellular fractions of hemopoietic, reticulo-endothelial or other systems, resulting in a functional defect of the organism.

urther investigations should be directed towards elaborating on the causes for the immediate and postponed death over the dose rate of 0-500 R. For this very reason the concept about the differentiated research on physiological systems, responsible for the

state of the organism during irradiation at sublethal doses [864] deserves attention, since their protection can require new methods and new principles.

This problem especially pertains to the range of small doses (0-30 R), in which even the "threshold" of the protection is projected on the chromosome rearrangements [293, 631, 632].

However should one consider the search of a means of protection at such a level of doses as the first assignment and to what degree this can be promising?

At first sight posed question may seen strange. Nevertheless, let us debate its validity.

The immediate somatical effects of single exposure at doses of 25-30 R are so small and transitory that there is hardly grounds for the development of special protective measures. Therefore, the protection from such doses can have merit only by taking into account their repeated exposure.

Conformable to the remote consequences of irradiation it is known that they hardly weaken the effect of protectors even during the action of considerably greater doses, when protection from immediate effects has been clearly expressed. Moreover, even the transplantation of bone marrow itself [23, 580] and in conjunction with protectors [580] does not guard against the development of tumors and the shortening of the lifespan. The reason for this phenomenon, in part may be the appearance of nonreparable and weakly protected damage of chromosomal complex in the majority of the somatical tissues with low proliferational activity. Nevertheless, one should expect some sort of effect of the protectors at small doses. Furthermore, at such small doses (up to 30 R) neither the experimental nor the greater development of remote consequences in man is indicative, and the presentations about its possible appearance are based only on the extrapolated data.

Finally, even with the clearly expressed protection from the chromosomal rehabilitation at small doses (25 R) the reduction in the number of cells with aberrations, for example, with 7 to 5% (see Chapter VII) can hardly be substantial for an organism.

However, one sphere of the effect of small doses remains, where the weakening of their effect is most advisable – this is the genetic apparatus of the sexual cells. Unfortunately, the majority of experimental investigations either confirm the lack of protection of the gonad, or report on the weakly expressed protective effect of the protectors. The research conducted by V. N. Ivanov and M. D. Pomerants together with us provides the proof of the indubitable protection of the testicles of mice using mexamine and its complex with cystaphos, although it is considerably less expressed than in the hemopoietic organs or intestines. Furthermore, the levels of doses, at which the protection has been detected, exceed the doses, called the threshold in the sense of protection, by ten times.

Apparently, one should heed the correct fundamental statement about the fact that protection of the heredity should be solved in new ways [631] and not only by a single one, and primarily during the chronic effect of small doses, aside from depending on the presence or absence of the threshold of effect of contemporary protectors.

The Dynamics of Radioresistance with Repeated Irradiations and Radiation Therapeutics

At present, one should consider it indisputable that the radioresistance of the bone marrow and intestines suffers phasal changes even in the shortest time following irradiation. During the first 6 h it is considerably intensified, then temporarily the radioresistance returns to the original level, and again gradually increases as a result of the initiation of the regenerative processes (from 15-18 h). The analysis of the ini. l reduction of radiosensitivity holds the greatest interest. It is necessary to explain

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whether it is the result of true restoration from sublethal damage, or by the variation in the undamaged part of the cells, the consequences of which are liquidated during the defined metabolic phase. Materialization of a form of reversed injury, a clarification of the connection of it with the damage of the chromosomes, interphasal disturbance or changes in the mitotic rhythmics will be required. It is also extremely interesting to explain possibility of random exposure for this process.

The presence of the phase dynamics of radioresistance takes on significant importance in radiation therapeutics of tumors. It is quite obvious that repeated irradiations, conducted without allowing for the possible change in the symptom of radiosensitivity of a tumor with time, can have the most undesirable consequences. The tendency towards synchronization of the division of tumoral cells is purposely advanced as one of the trends for increasing the effectiveness of radiation therapeutics [864].

Specific interest in this plan represents the utilization of loaded high energy particles, containing a section of high specific ionization (Bragg's peak) at the end of the path, started at present based on the initiative of Professor A. I. Ruderman at the Institute of Experimental and Clinical Oncology, Academy of Medical Sciences, USSR. As it was shown, under an exposure with rapid neutrons also with existing densely ionizing particles, the change in radioresistance in the early postradiation period [556], as well as with the decrease in the dose rate [534] does not take place. In fact, with the application of loaded particles the utilization of protectors, taking into account their preferential effect on normal cells becomes especially promising, if one keeps in mind the weakening of the protective effect within the range of the tumor, where Bragg's peak, consisting of densely ionizing particles, will be concentrated.

Separation of Chromosomal Damage and the Hygienic Normalization of Ionizing Radiation

The contemporary principles of hygienic normalization of ionizing radiation, accepted by the [ICRP] (MKP3) International Commission on

Radiological Protection, are based on the presentation about the nonthreshold ability of a genetic radiation effect, and therefore is included as a "reasonable risk" in the possible appearance of tumors. The data about the nonthreshold ability mutational effect of radiation were obtained by an extrapolating means, because with action from the least possible (within the limits of accuracy of contemporary dosimetric methods) levels of radiation and higher, the mutational effect increases linearly depending on the dose.

At the same time irrefutable facts have been received at present about the possibility of restoration due to the genetic damage or the dependences of their appearance on the dose rate [477]. Very thorough investigations were conducted by Russell, who has for the first time, reliably maintained the effect of the intensity of irradiation on the occurrence of mutations in the animals. However, also in the works of Russell, where spermatogonia of the mice were irradiated at dose rate of 0.001 rad/min, the occurrence of mutations was higher than in the control. The author based on this drew the conclusion that an elusive threshold of radiation intensity exists, even at such a dose rate, where based on his information, there was a minimum for laboratory tests with the occurrence of mutations in the animals [492].

In our conducted experiments in the research on the dynamics of the appearance of chromosomal aberrations in quiescent cells of the liver with the application of approximately the same dose rate (0.00116 rad/min) the disappearance of aberrations also considerably exceeded the disappearance of aberrations in the control. However, with its decrease by approximately 2 times (0.00058 rad/min) these differences were not observed; number of cells with aberrations in the chromosomes in the animals undergoing irradiation at such an intensity during a half of the year, an increase, however, was not discernible from those observed in the intact control animals. In the investigations conducted independent of ours [530, 534] and in more recent ones [535], reparation of the chromosomal damage in quiescent cells of the liver were also shown, with fractionated

irradiation using sizable doses (7 R per twenty-four hour period) and at a high dose rate. Therefore, the authors of these investigations were not able to observe the phenomena we revealed.

The urge to draw a conclusion about the practical existence of a threshold in the appearance of a mutation, at least, for chromosomal rehabilitation, just as observed for all the remaining physiological reactions on radiation exposure, is conducive for the further development of similar investigations.

One ought to take into account that the doses we used are almost exceeded by 20 times the accepted maximum permissible amounts of radiation for man. The latter, however, were calculated in order to obtain doses during a 6 h working day, i.e., at the highest intensity of exposure and in the presence of long interruptions. Obviously, it is expediently to take into account these features in the planning of corresponding experiments.

Finally, the data about the increase in the lifespan at a low intensity of irradiation require a reasonable interpretation [615, 865-867].

The biological effect of small doses and chronic irradiations on the genetic apparatus of sexual and somatical cells was comprehensively examined by us as well as by Ya. L. Glembotskiy in a special survey [870], where the entire imperfection of the contemporary state of this agitating problem was convincingly shown.

Here, we wanted only to emphasize the need for a further concrete definition of the presentations on temporary and quantitative parameters of the danger of ionizing radiation for the proper construction of the principles of antiradiation protection.

These problems are dictated by the rapid technical progress and the broad introduction of atomic energy into all fields of life on earth associated with it, but in the near future also beyond its

limits. All this, doubtlessly, will place hygienic science ahead of the need for a strict registration of characteristics of various forms and conditions of radiation exposure, and possibly, the known overestimate of the significance of the radiation factor in comparison with numerous factors of the environment, primarily for the restricted professional contingents.

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13. ABSTRACT

In the monograph extensive material from the investigations by the author and source material on biological shielding from ionizing radiation have been generalized. Using a cytokaryological analysis of the damage and protection of the bone marrow, convincing proof is presented that the mechanism of anti-radiation protection is the consequence of weakening of the ititial damage of critical systems in the organism. Examined in detail for the first time is the possibility of modifying the effect of various forms of low level ionizing radiation (X-rays, gamma-quantum and protons of high energies) with single exposure fractionated and chronic irradiations. Attempt was made to analyze the dependence of damage and protection of the hereditary apparatus of somatical cells on the distribution of the radiation dosage with time and to evaluate the role of this phenomenon for the immediate and remote effects of irradiation. The distinctive feature of this book is its practical objectivity of posed problems (application of protective means by man, principles of the hydienic standardization of the radiation factor, etc.). A wide circle of pertinent problems, their actuality, the critical examination of extensive material from investigations of the author and source materials were calculated primarily for specialists, studying biological radiation effects, and for students of advanced courses corresponding to the college level.

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